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(54) Title: INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

(57) Abstract: The present invention is directed to compounds which inhibit prenyl-protein transferase and the prenylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting prenyl-protein transferase and the prenylation of the oncogene protein Ras.



WO 01/17992 A1

TITLE OF THE INVENTION

INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

5 The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange
10 GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers,
15 including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with
20 Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-
25 protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. Such enzymes may be generally termed prenyl-protein transferases. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are
30 known to undergo post-translational farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins
35 of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993)). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995)).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of poly-isoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically

reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

5 It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

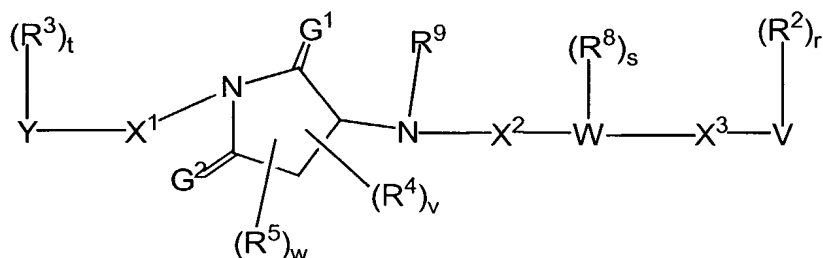
10 It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1). It has also been disclosed that certain compounds which incorporate a pyrrolidine moiety are inhibitors of FPTase (WO 97/37900, and U.S. Patent Nos. 5,627,202
15 and 5,661,161).

It is, therefore, an object of this invention to develop compounds that will inhibit prenyl-protein transferase and thus, the post-translational isoprenylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing
20 the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises non-prodrug compounds which inhibit prenyl-protein transferases. Further contained in this invention are chemotherapeutic compositions containing these prenyl-protein transferase inhibitors and
25 methods for their production.

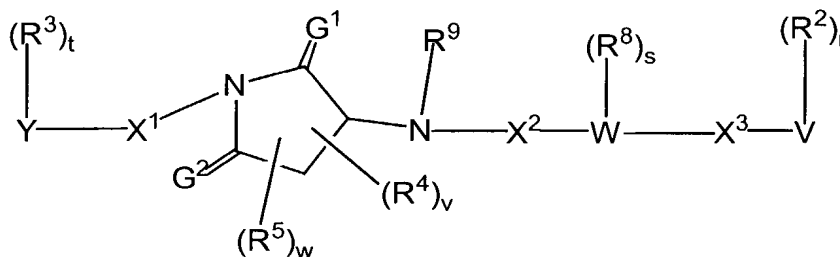
The compounds of this invention are illustrated by the formula A:



A

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of prenyl-protein transferase. In a first embodiment of this invention, the inhibitors of a prenyl-protein transferase are illustrated by the formula A:



A

5

wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

10 X^2 is $(C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_p$;

X^3 is $(C(R^{1c})_2)_q A^4 (C(R^{1c})_2)_q$;

R^{1a} , R^{1b} and R^{1c} are independently selected from:

- 15 a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and
- 20 c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$,
- 25

$-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$, $\text{R}^{10}\text{C}(\text{O})-$,
 $\text{R}^{10}\text{OC}(\text{O})-$, halo, $-\text{N}(\text{R}^{10})_2$, and $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$;

A^1 , A^3 and A^4 are independently selected from

- 5 a) a bond,
- b) $-\text{C}(=\text{O})-$,
- c) $-\text{HC}=\text{CH}-$,
- d) $-\text{C}\equiv\text{C}-$,
- e) O,
- 10 f) NR^{10} ,
- g) $\text{NR}^{10}\text{C}(\text{O})$,
- h) $\text{C}(\text{O})\text{NR}^{10}$,
- i) $\text{OC}(\text{O})\text{NR}^{10}$,
- j) $\text{NR}^{10}\text{C}(\text{O})\text{O}$,
- 15 k) $\text{S}(=\text{O})_m$,
- l) $\text{C}(\text{O})\text{O}$, and
- m) $\text{OC}(\text{O})$;

A^2 is selected from

- 20 a) a bond,
- b) $-\text{C}(=\text{O})-$,
- c) $\text{NR}^{10}\text{C}(\text{O})$,
- d) $\text{S}(=\text{O})_m$, and
- e) $\text{OC}(\text{O})$;

25

R^2 is independently selected from:

- a) hydrogen,
- b) CN,
- c) NO_2 ,
- 30 d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- g) C_1 - C_6 alkyl, unsubstituted or substituted,
- h) OR^{10} ,

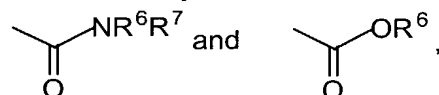
- i) N_3 ,
 j) $R^{6a}S(O)_m$,
 k) C_3-C_{10} cycloalkyl, unsubstituted or substituted,
 l) C_2-C_6 alkenyl, unsubstituted or substituted,
 5 m) C_2-C_6 alkynyl, unsubstituted or substituted,
 n) $(R^{10})_2NC(O)NR^{10}-$,
 o) $R^{10}C(O)-$,
 p) $R^{10}C(O)NR^{10}-$,
 q) $R^{10}OC(O)-$,
 10 r) $-N(R^{10})_2$,
 s) $R^{10}OC(O)NR^{10}-$, and
 t) $-(C_1-C_6 \text{ alkyl})NR^{10}C(O)R^{13}$;

R^3 is independently selected from:

- 15 H, CN, NO_2 , halo, unsubstituted or substituted C_1-C_6 alkyl, N_3 , oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclylalkyl, C_1-C_6 perfluoroalkyl, CF_3O- , CF_3CH_2- , unsubstituted or
 20 substituted C_3-C_{10} cycloalkyl, OR^{10} , NR^6R^7 , OR^6 , $-C(O)R^{10}$, $-O(C_1-C_6$
 alkyl) OR^{10} , $-S(O)_mR^{6a}$, $-OS(O)_mR^{6a}$, $-C(O)NR^6R^7$, $-NHC(O)R^{10}$, $-(C_1-C_6$
 alkyl) OR^{10} , and $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

R^4 and R^5 are independently selected from:

- 25 H, OR^{10} , unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted
 C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or
 substituted aryl, unsubstituted or substituted heterocycle,

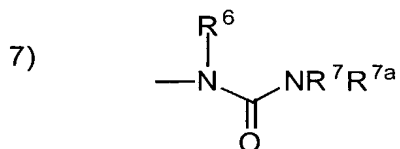
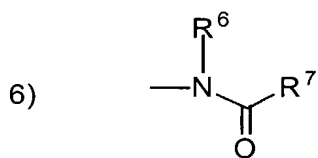


wherein the substituted group is substituted with one or more of:

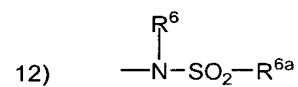
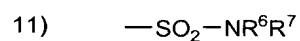
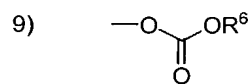
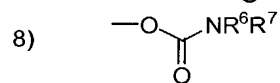
- 30 1) aryl or heterocycle, unsubstituted or substituted with:
 a) C_1-C_6 alkyl,
 b) $(CH_2)_nOR^6$,

5

- c) $(\text{CH}_2)_n \text{NR}^6 \text{R}^7$,
 d) halogen,
 e) CN,
 f) aryl or heteroaryl,
 g) perfluoro- C_1 - C_4 alkyl,
 h) $\text{S}(\text{O})_m \text{R}^{6a}$,

2) C_3 - C_6 cycloalkyl,3) OR^6 ,4) $\text{S}(\text{O})_m \text{R}^{6a}$,5) $-\text{NR}^6 \text{R}^7$,

10



- 15) N_3 ,
- 16) halo, and
- 17) perfluoro- C_{1-4} -alkyl; or

5 R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;


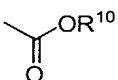
and any of R^4 and R^5 are optionally attached to the same carbon atom;

10

R^6 , R^7 and R^{7a} are independently selected from:

H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

15

- a) C_1-C_6 alkoxy,
- b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- c) halogen,
- d) HO,
- e)  ,
- f)  ,
- g) $-S(O)_mR^{6a}$, or
- h) $N(R^{10})_2$; or

20

R^6 and R^7 may be joined in a ring;

25 R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

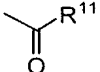
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- 1) C_{1-4} alkoxy,

2) aryl or heterocycle,

3) halogen,

4) HO,

5) ,

5

6) SO₂R^{6a},

7) N(R¹⁰)₆; and

b) C₁-C₆ alkyl, unsubstituted or substituted with one or more of the following:

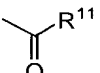
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1) -C(R¹⁰)₂C₁₋₄ alkoxy,

2) aryl or heterocycle,

3) -C(R¹⁰)₂halogen,

4) -C(R¹⁰)₂OH,

5) ,

15

6) -C(R¹⁰)₂SO₂R^{6a}, and

7) -C(R¹⁰)₂N(R¹⁰)₂;

R⁸ is independently selected from

20

a) hydrogen,

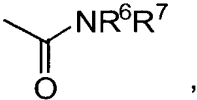
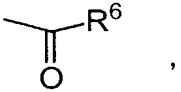
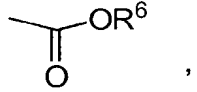
b) unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted C₃-C₆ cycloalkyl, unsubstituted or substituted C₁-C₄ perfluoroalkyl, F, Cl, Br, R¹⁰O-, CN, R^{6a}S(O)_m-, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, NO₂, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, R¹⁰OC(O)NR¹⁰-, N₃, or -N(R¹⁰)₂, and

25

c) C₁-C₆ alkyl, unsubstituted or substituted by C₁-C₄ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R^{6a}S(O)_m-, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

30

R⁹ is independently selected from

- 1) H, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₈ alkenyl, unsubstituted or substituted C₂-C₈ alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- 5 a) C₁-C₆ alkyl, unsubstituted or substituted,
 b) (CH₂)_nOR⁶,
 c) (CH₂)_nNR⁶R⁷,
 d) halogen,
 10 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro-C₁-C₄ alkyl,
 i) S(O)_mR^{6a},
 15 j) N(R¹⁰)₂,
 k) NR¹⁰C(O)R¹¹,
 l) NR¹⁰C(O)R¹¹N(R¹⁰)₂,
 m) -R¹⁰(CH₂)_nR¹¹,
- 2) C₃-C₆ cycloalkyl,
 20 3) S(O)_mR^{6a},
 4) ,
 5) -SO₂-NR⁶R⁷ ,
 6) ,
 7) , and
 8) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³ ;

R¹⁰ is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted C₁-C₆ alkyl,
- c) C₃-C₆ cycloalkyl,
- 5 d) 2,2,2-trifluoroethyl,
- e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclylalkyl;

10

R¹¹ is independently selected from

- a) unsubstituted or substituted C₁-C₆ alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- 15 d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclylalkyl;

R¹³ is independently selected from

- a) H,
- 20 b) unsubstituted or substituted C₁-C₆ alkyl,
- c) unsubstituted or substituted aryl,
- d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclylalkyl, unsubstituted or substituted,
- 25 g) C₂-C₆ alkynyl, unsubstituted or substituted,
- h) C₂-C₆ alkenyl, unsubstituted or substituted,
- i) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
- j) CF₃,
- k) CF₃O-,
- 30 l) CF₃CH₂-,
- m) OR¹⁰,
- n) -C(O)R¹⁰,
- o) -O(C₁-C₆ alkyl)OR¹⁰,
- p) -C(O)NR⁶R⁷,

- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 and G^2 are independently selected from oxygen or H_2 ;

5

V is selected from

- a) hydrogen,
 b) heterocycle,
 c) aryl,
 10 d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a
 heteroatom selected from O, $S(O)_m$, and N, and
 e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^4 is $S(O)_m$ and q is 0;

15 W is a heterocycle;

Y is selected from

- a) H,
 b) C_1-C_8 alkyl,
 20 c) C_2-C_8 alkenyl,
 d) C_2-C_8 alkynyl,
 e) C_3-C_{20} cycloalkyl,
 f) aryl, and
 g) heterocycle;

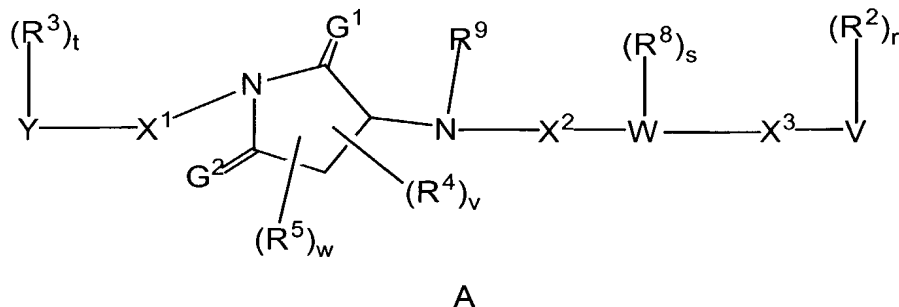
25

- m is 0, 1 or 2;
 n is 0, 1, 2, 3, 4, 5 or 6;
 p is 0, 1, 2, 3, 4, 5 or 6;
 q is 0, 1, 2, 3, 4, 5 or 6;
 30 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and

w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

5 Another embodiment of the compounds of this invention is illustrated by formula A:



wherein

10 X^1 is $(C(R^{1c})_2)_n A^1 (C(R^{1c})_2)_n A^2$;

X^2 is $(C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_p$;

X^3 is $(C(R^{1c})_2)_q A^4$;

15

R^{1a} and R^{1b} are independently selected from:

- a) hydrogen;
 - b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and
 - c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or
- 20
- 25

substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

5

R^{1c} is selected from

- a) hydrogen and
- b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted

10

aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

15

A^1 and A^3 are independently selected from

- a) a bond,
- b) $-C(=O)$ -,
- c) O,
- d) NR^{10} ,
- e) $NR^{10}C(O)$,
- f) $C(O)NR^{10}$,
- g) $OC(O)NR^{10}$,
- h) $NR^{10}C(O)O$,
- i) $S(=O)_m$,
- j) $OC(O)$, and
- k) $C(O)O$;

20

25

A^2 is selected from

30

- a) a bond,
- b) $-C(=O)$ -,
- c) $NR^{10}C(O)$, and
- d) $S(=O)_m$;

A⁴ is a bond;

R² is independently selected from:

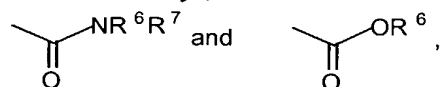
- a) hydrogen,
- 5 b) CN,
- c) NO₂,
- d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- 10 g) C₁-C₆ alkyl, unsubstituted or substituted,
- h) OR¹⁰,
- i) N₃,
- j) R^{6a}S(O)_m,
- k) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
- 15 l) C₂-C₆ alkenyl, unsubstituted or substituted,
- m) C₂-C₆ alkynyl, unsubstituted or substituted,
- n) (R¹⁰)₂NC(O)NR¹⁰-,
- o) R¹⁰C(O)-,
- p) R¹⁰C(O)NR¹⁰-,
- 20 q) R¹⁰OC(O)-,
- r) -N(R¹⁰)₂,
- s) R¹⁰OC(O)NR¹⁰-, and
- t) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³;

25 R³ is independently selected from:

- H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 30 heterocyclylalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -OS(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆
 alkyl)OR¹⁰, and -(C₁-C₆ alkyl)C(O)R¹⁰;

R^4 and R^5 are independently selected from:

H, OR^{10} , unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

a) C_1-C_6 alkyl,

b) $(CH_2)_n OR^6$,

10 c) $(CH_2)_n NR^6 R^7$,

d) halogen,

e) CN,

f) aryl or heteroaryl,

g) perfluoro- C_1-C_4 alkyl,

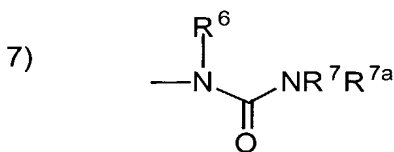
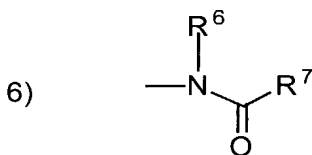
15 h) $S(O)_m R^{6a}$,

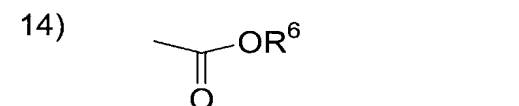
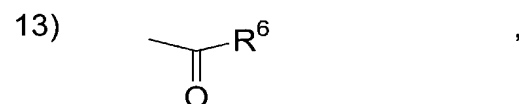
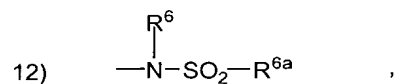
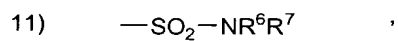
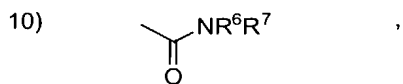
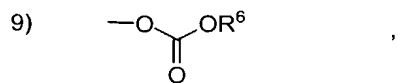
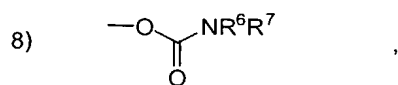
2) C_3-C_6 cycloalkyl,

3) OR^6 ,

4) $S(O)_m R^{6a}$,

5) $-NR^6 R^7$,





15) N_3 ,

16) halo, and

17) perfluoro- C_{1-4} -alkyl; or

5

R^4 and R^5 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$

wherein one of the carbon atoms is optionally replaced by a moiety selected from:

10 O, S(O)_m , NR^{10} , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:


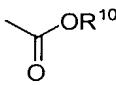
15 H, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, $\text{C}_1\text{—C}_4$ perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

a) $\text{C}_1\text{—C}_6$ alkoxy,

b) substituted or unsubstituted aryl or substituted or
20 unsubstituted heterocycle,

c) halogen,

20

- d) HO,
- e) ,
- f) ,
- g) $-\text{S}(\text{O})_m\text{R}^{6a}$, or
- h) $\text{N}(\text{R}^{10})_2$; or

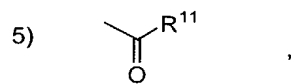
5 R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

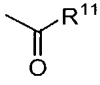
10 a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 15 4) HO,



- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

20 b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of the following:

- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 25 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

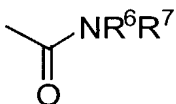
- a) hydrogen,
- b) unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6 alkynyl, unsubstituted or substituted C_3-C_6 cycloalkyl, unsubstituted or substituted C_1-C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O-$, CN, $R^{6a}S(O)_m-$, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}-$, NO_2 , $(R^{10})_2NC(O)NR^{10}-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, $R^{10}OC(O)NR^{10}-$, N_3 , or $-N(R^{10})_2$, and
- c) C_1-C_6 alkyl, unsubstituted or substituted by C_1-C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{6a}S(O)_m-$, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2NC(O)NR^{10}-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}-$;

R^9 is independently selected from

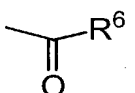
- 1) H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
 - a) C_1-C_6 alkyl, unsubstituted or substituted,
 - b) $(CH_2)_nOR^6$,
 - c) $(CH_2)_nNR^6R^7$,
 - d) halogen,
 - e) CN,
 - f) aryl, unsubstituted or substituted,
 - g) heterocycle, unsubstituted or substituted,
 - h) perfluoro- C_1-C_4 alkyl,
 - i) $S(O)_mR^{6a}$,
 - j) $N(R^{10})_2$,
 - k) $NR^{10}C(O)R^{11}$,
 - l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 - m) $-R^{10}(CH_2)_nR^{11}$,

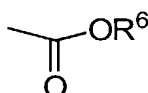
2) C₃-C₆ cycloalkyl,

3) S(O)_mR^{6a},

4) ,

5) —SO₂—NR⁶R⁷ ,

6) ,

7) , and

5

8) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³ ;

R¹⁰ is independently selected from

- 10
- a) hydrogen,
 - b) unsubstituted or substituted C₁-C₆ alkyl,
 - c) C₃-C₆ cycloalkyl,
 - d) 2,2,2-trifluoroethyl,
 - e) unsubstituted or substituted heteroaryl,
 - f) unsubstituted or substituted aryl,
 - 15 g) unsubstituted or substituted aralkyl, and
 - h) unsubstituted or substituted heterocyclalkyl;

R¹¹ is independently selected from

- 20
- a) unsubstituted or substituted C₁-C₆ alkyl,
 - b) unsubstituted or substituted aralkyl,
 - c) unsubstituted or substituted heterocycle,
 - d) unsubstituted or substituted aryl, and
 - e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted C_1 - C_6 alkyl,
- c) unsubstituted or substituted aryl,
- 5 d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclalkyl, unsubstituted or substituted,
- g) C_2 - C_6 alkynyl, unsubstituted or substituted,
- h) C_2 - C_6 alkenyl, unsubstituted or substituted,
- 10 i) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
- j) CF_3 ,
- k) CF_3O- ,
- l) CF_3CH_2- ,
- m) OR^{10} ,
- 15 n) $-C(O)R^{10}$,
- o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
- p) $-C(O)NR^6R^7$,
- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
- r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

20

G^1 and G^2 are independently selected from oxygen or H_2 ;

V is selected from

- a) heterocycle,
- 25 b) aryl, and
- c) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, $S(O)_m$, and N, and

W is a heterocycle;

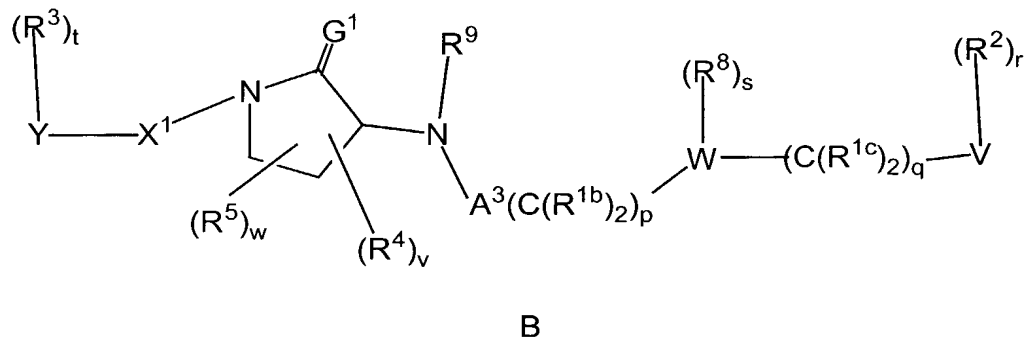
30

Y is selected from

- a) H,
- b) C_1 - C_8 alkyl,
- c) C_3 - C_{20} cycloalkyl,

- d) aryl, or
e) heterocycle;
- m is 0, 1 or 2;
5 n is 0, 1, 2, 3, 4, 5 or 6;
p is 0, 1, 2, 3, 4, 5 or 6;
q is 0, 1, 2, or 3;
r is 0 to 5;
s is 0, 1, 2, 3 or 4;
10 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
u is 4 or 5;
v is 0, 1, 2, 3 or 4; and
w is 0, 1, 2, 3 or 4;
- 15 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

Another embodiment of the compounds of this invention is illustrated by the formula B:



- 20 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- 25 a) hydrogen;

- 5 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀ cycloalkyl, R¹⁰O-, R^{6a}S(O)_m, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, -N(R¹⁰)₂, R¹⁰OC(O)-, and R¹⁰OC(O)NR¹⁰-, and
- 10 c) unsubstituted or substituted C₁-C₆ alkyl, wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, R¹⁰C(O)NR¹⁰-, -C(O)NR⁶R⁷, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

R^{1b} and R^{1c} are independently selected from

- 15 a) hydrogen and
- b) unsubstituted or substituted C₁-C₆ alkyl, wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, R¹⁰C(O)NR¹⁰-, -C(O)NR⁶R⁷, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;
- 20

A¹ is selected from

- 25 a) a bond,
- b) -C(=O)-,
- c) O,
- d) NR¹⁰,
- e) NR¹⁰C(O),
- 30 f) C(O)NR¹⁰,
- g) OC(O)NR¹⁰,
- h) NR¹⁰C(O)O,
- i) S(=O)_m,
- j) C(O)O, and

k) $\text{OC(O)};$

A^2 is selected from

- 5 a) a bond,
 b) $-\text{C(=O)}-$,
 c) $\text{NR}^{10}\text{C(O)}$, and
 d) S(=O)_m ;

A^3 is selected from a bond or C(=O) ;

10

R^2 is independently selected from:

- a) hydrogen,
 b) CN ,
 c) NO_2 ,
 15 d) halogen,
 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
 h) OR^{10} ,
 20 i) N_3 ,
 j) $\text{R}^{6a}\text{S(O)}_m$,
 k) $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted,
 l) $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted,
 m) $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted,
 25 n) $(\text{R}^{10})_2\text{NC(O)NR}^{10}-$,
 o) $\text{R}^{10}\text{C(O)}-$,
 p) $\text{R}^{10}\text{C(O)NR}^{10}-$,
 q) $\text{R}^{10}\text{OC(O)}-$,
 r) $-\text{N(R}^{10})_2$,
 30 s) $\text{R}^{10}\text{OC(O)NR}^{10}-$, and
 t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C(O)R}^{13}$;

R^3 is independently selected from:

H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclylalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 5 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰,
 and -(C₁-C₆ alkyl)C(O)R¹⁰;

10 R⁴ and R⁵ are independently selected from:

H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted
 aryl, unsubstituted or substituted heterocycle, wherein the substituted group is
 substituted with one or more of:

15 1) aryl or heterocycle, unsubstituted or substituted with:

- a) C₁-C₆ alkyl,
 b) (CH₂)_nOR⁶,
 c) (CH₂)_nNR⁶R⁷,
 d) halogen,
 e) CN,
 20 f) aryl or heteroaryl,
 g) perfluoro-C₁-C₄ alkyl,
 h) S(O)_mR^{6a},

2) C₃-C₆ cycloalkyl,

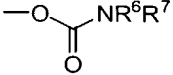
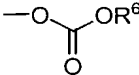
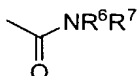
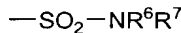
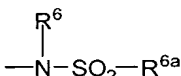
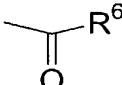
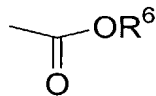
3) OR⁶,

25 4) S(O)_mR^{6a},

5) —NR⁶R⁷ ,

6)
$$\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C—R}^7 \\ || \\ \text{O} \end{array}$$
 ,

7)
$$\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—C—NR}^7\text{R}^{7a} \\ || \\ \text{O} \end{array}$$
 ,


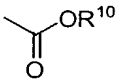
- 8)  ,
- 9)  ,
- 10)  ,
- 11)  ,
- 12)  ,
- 13)  ,
- 14)  ,
- 15) N₃,
- 16) halo, and
- 17) perfluoro-C₁₋₄-alkyl; or

5

R⁴ and R⁵ are attached to the same C atom and are combined to form -(CH₂)_u-
 wherein one of the carbon atoms is optionally replaced by a moiety selected from:
 10 O, S(O)_m, NR¹⁰, -NC(O)-, and -N(COR¹⁰)-;

and any of R⁴ and R⁵ are optionally attached to the same carbon atom;

15 R⁶, R⁷ and R^{7a} are independently selected from:
 H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl,
 arylsulfonyl, heteroarylsulfonyl, C₁-C₄ perfluoroalkyl, unsubstituted or
 substituted with one or two substituents selected from:
 a) C₁-C₆ alkoxy,
 b) substituted or unsubstituted aryl or substituted or
 20 unsubstituted heterocycle,

- c) halogen,
- d) HO,
- e) ,
- f) ,
- g) $-\text{S}(\text{O})_m\text{R}^{6a}$, or
- h) $\text{N}(\text{R}^{10})_2$; or

5

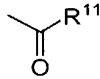
R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

10 R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

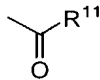
15

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) HO,
- 5) ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

20

b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of the following:

25

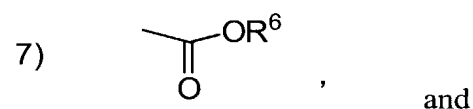
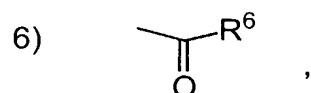
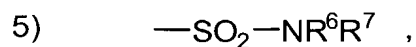
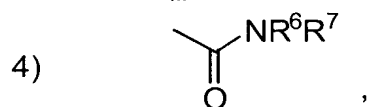
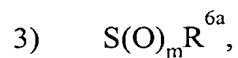
- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted
 C_2 - C_6 alkynyl, unsubstituted or substituted C_3 - C_6 cycloalkyl,
 unsubstituted or substituted C_1 - C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O$ -,
 CN, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, NO_2 , $(R^{10})_2NC(O)NR^{10}$ -,
 $R^{10}C(O)$ -, $R^{10}OC(O)$ -, $R^{10}OC(O)NR^{10}$ -, N_3 , or $-N(R^{10})_2$, and
 c) C_1 - C_6 alkyl, unsubstituted or substituted by C_1 - C_4 perfluoroalkyl,
 F, Cl, Br, $R^{10}O$ -, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, CN,
 $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, N_3 , $-N(R^{10})_2$, and
 $R^{10}OC(O)NR^{10}$ -;

R^9 is independently selected from

- 15 1) H, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or
 substituted C_2 - C_8 alkenyl, unsubstituted or substituted C_2 - C_8 alkynyl,
 unsubstituted or substituted aryl, and unsubstituted or substituted
 heterocycle, wherein the substituted group is substituted with one or
 more of:
 a) C_1 - C_6 alkyl, unsubstituted or substituted,
 b) $(CH_2)_nOR^6$,
 c) $(CH_2)_nNR^6R^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1 - C_4 alkyl,
 i) $S(O)_mR^{6a}$,
 j) $N(R^{10})_2$,
 k) $NR^{10}C(O)R^{11}$,
 l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 m) $-R^{10}(CH_2)_nR^{11}$,
 2) C_3 - C_6 cycloalkyl,



5

R^{10} is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
- c) $\text{C}_3\text{-C}_6$ cycloalkyl,
- 10 d) 2,2,2-trifluoroethyl,
- e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

15

R^{11} is independently selected from

- a) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- 20 d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,

- b) unsubstituted or substituted C_1 - C_6 alkyl,
 c) unsubstituted or substituted aryl,
 d) unsubstituted or substituted heterocycle,
 e) aralkyl, unsubstituted or substituted,
 5 f) heterocyclalkyl, unsubstituted or substituted,
 g) C_2 - C_6 alkynyl, unsubstituted or substituted,
 h) C_2 - C_6 alkenyl, unsubstituted or substituted,
 i) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
 j) CF_3 ,
 10 k) CF_3O- ,
 l) CF_3CH_2- ,
 m) OR^{10} ,
 n) $-C(O)R^{10}$,
 o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
 15 p) $-C(O)NR^6R^7$,
 q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 is selected from oxygen or H_2 ;

20

V is aryl or heteroaryl;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl;

25

Y is selected from

- a) H,
 b) C_1 - C_8 alkyl,
 c) C_3 - C_{20} cycloalkyl,
 30 d) aryl or
 e) heterocycle;

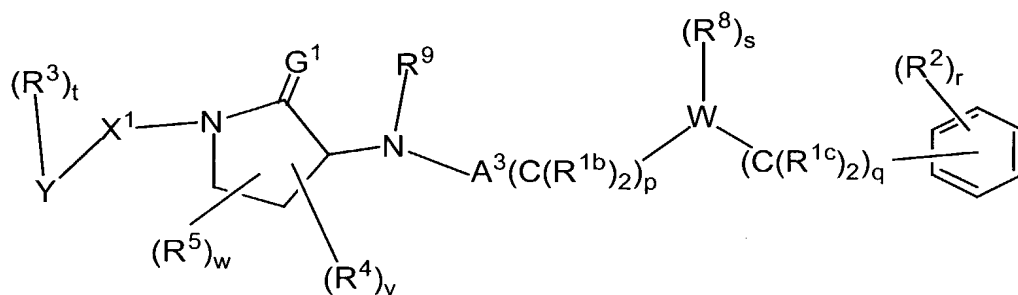
m is 0, 1 or 2;

n is 0, 1, 2, 3, 4, 5 or 6;

- p is 0, 1, 2, 3, or 4;
 q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 5 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

10 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

Another embodiment of the compounds of this invention is illustrated by the formula C:



C

15 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- 20 a) hydrogen;
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$,
 25 $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and

- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
 b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

A^1 is selected from

- a) a bond,
 b) $-C(=O)$ -,
 c) O,
 d) NR^{10} ,
 e) $NR^{10}C(O)$,
 f) $C(O)NR^{10}$,
 g) $OC(O)NR^{10}$,
 h) $NR^{10}C(O)O$,
 i) $S(=O)_m$,
 j) $C(O)O$, and
 k) $OC(O)$;

A^2 is selected from

- a) a bond,
 b) $-C(=O)$ -,

- c) $\text{NR}^{10}\text{C}(\text{O})$, and
- d) $\text{S}(=\text{O})_m$;

A^3 is selected from

- 5 a) a bond, or
- b) $\text{C}(=\text{O})$;

R^2 is independently selected from:

- a) hydrogen,
- 10 b) CN ,
- c) NO_2 ,
- d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- 15 g) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
- h) OR^{10} ,
- i) N_3 ,
- j) $\text{R}^{6a}\text{S}(\text{O})_m$,
- k) $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted,
- 20 l) $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted,
- m) $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted,
- n) $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$,
- o) $\text{R}^{10}\text{C}(\text{O})-$,
- p) $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$,
- 25 q) $\text{R}^{10}\text{OC}(\text{O})-$,
- r) $-\text{N}(\text{R}^{10})_2$,
- s) $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$, and
- t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C}(\text{O})\text{R}^{13}$;

30 R^3 is independently selected from:

H, CN, NO_2 , halo, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, N_3 , oxido, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted

heterocyclalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆ alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰, and -(C₁-C₆ alkyl)C(O)R¹⁰;

5

R⁴ and R⁵ are independently selected from:

H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:

10

1) aryl or heterocycle, unsubstituted or substituted with:

a) C₁-C₆ alkyl,

b) (CH₂)_nOR⁶,

c) (CH₂)_nNR⁶R⁷,

d) halogen,

15

e) CN,

f) aryl or heteroaryl,

g) perfluoro-C₁-C₄ alkyl,

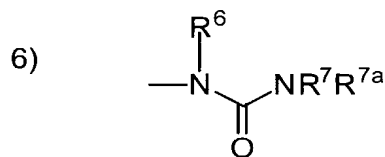
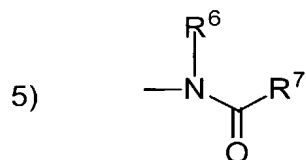
h) S(O)_mR^{6a},

2) C₃-C₆ cycloalkyl,

20

3) OR⁶,

4) —NR⁶R⁷,



8) halo, and

9) perfluoro-C₁-4-alkyl; or


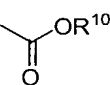
R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, NR^{10} , $-NC(O)-$, and $-N(COR^{10})-$;

5

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

10 H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

- 15 a) C_1-C_6 alkoxy,
 b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
 c) halogen,
 d) HO,
 e) ,
 f) ,
 g) $-S(O)_mR^{6a}$, or
 h) $N(R^{10})_2$; or

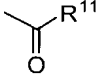
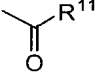
20 R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

25 a) C_3-6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

- 30 1) C_{1-4} alkoxy,
 2) aryl or heterocycle,
 3) halogen,
 4) HO,

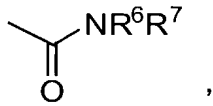
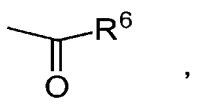
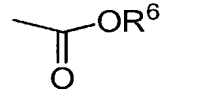
- 5)  ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and
- b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of
- 5 the following:
- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 10 5)  ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

- 15 a) hydrogen,
- b) F, Cl, Br, $\text{R}^{10}\text{O}-$, CN , $\text{R}^{6a}\text{S}(\text{O})_m-$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, NO_2 , $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$, N_3 , or $-\text{N}(\text{R}^{10})_2$, and
- c) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted by $\text{C}_1\text{-C}_4$ perfluoroalkyl,
- 20 F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{6a}\text{S}(\text{O})_m-$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN , $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, and $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$;

R^9 is independently selected from

- 25 1) H, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted $\text{C}_2\text{-C}_8$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_8$ alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- 30 a) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
- b) $(\text{CH}_2)_n\text{OR}^6$,

- 5
- c) $(\text{CH}_2)_n \text{NR}^6 \text{R}^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1 - C_4 alkyl,
 i) $\text{S}(\text{O})_m \text{R}^{6a}$,
 j) $\text{N}(\text{R}^{10})_2$,
 k) $\text{NR}^{10} \text{C}(\text{O}) \text{R}^{11}$,
 10 l) $\text{NR}^{10} \text{C}(\text{O}) \text{R}^{11} \text{N}(\text{R}^{10})_2$,
 m) $-\text{R}^{10}(\text{CH}_2)_n \text{R}^{11}$,
 2) C_3 - C_6 cycloalkyl,
 3) $\text{S}(\text{O})_m \text{R}^{6a}$,
 4) ,
 5) $-\text{SO}_2-\text{NR}^6 \text{R}^7$,
 6) ,
 7) , and
 15 8) $-(\text{C}_1\text{-C}_6 \text{ alkyl}) \text{NR}^{10} \text{C}(\text{O}) \text{R}^{13}$;

R^{10} is independently selected from

- 20 a) hydrogen,
 b) unsubstituted or substituted C_1 - C_6 alkyl,
 c) C_3 - C_6 cycloalkyl,
 d) 2,2,2-trifluoroethyl,
 e) unsubstituted or substituted heteroaryl,
 f) unsubstituted or substituted aryl,

- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

R^{11} is independently selected from

- 5 a) unsubstituted or substituted C_1 - C_6 alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclalkyl;

10

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted C_1 - C_6 alkyl,
- c) unsubstituted or substituted aryl,
- 15 d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclalkyl, unsubstituted or substituted,
- g) C_2 - C_6 alkynyl, unsubstituted or substituted,
- h) C_2 - C_6 alkenyl, unsubstituted or substituted,
- 20 i) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
- j) CF_3 ,
- k) CF_3O- ,
- l) CF_3CH_2- ,
- m) OR^{10} ,
- 25 n) $-C(O)R^{10}$,
- o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
- p) $-C(O)NR^6R^7$,
- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
- r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

30

G^1 is selected from oxygen or H_2 ;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl;

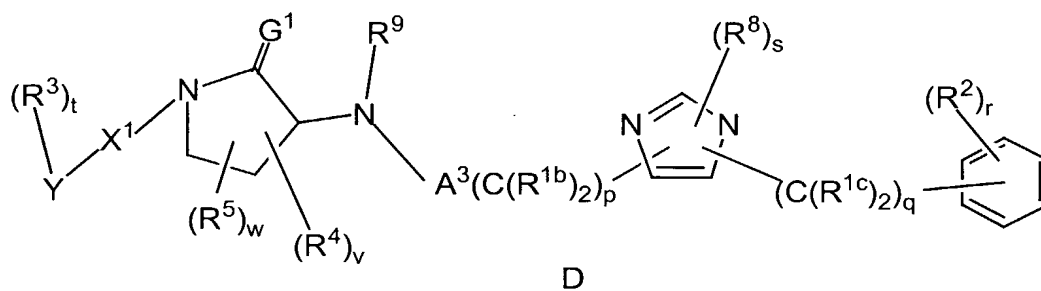
Y is selected from

- 5 a) H,
 b) C₁-C₈ alkyl,
 c) C₃-C₂₀ cycloalkyl,
 d) aryl, or
 e) heterocycle;

- 10 m is 0, 1 or 2;
 n is 0, 1, 2, 3, 4, 5 or 6;
 p is 0, 1, 2, 3, or 4;
 q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

- 20 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

Another embodiment of the compounds of this invention is illustrated by formula D:



- 25 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)(NR^{10})$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -; and
- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
- b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)(NR^{10})$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

A^1 is selected from

- a) a bond,
- b) $-C(=O)$ -,
- c) O,
- d) NR^{10} ,
- e) $NR^{10}C(O)$,
- f) $C(O)NR^{10}$,

- g) OC(O)NR^{10} ,
 h) $\text{NR}^{10}\text{C(O)O}$,
 i) S(=O)_m ,
 j) C(O)O , and
 5 k) OC(O) ;

A^2 is selected from

- a) a bond,
 b) $-\text{C(=O)}-$,
 10 c) $\text{NR}^{10}\text{C(O)}$, and
 d) S(=O)_m ;

A^3 is selected from

- a) a bond or
 15 b) C(=O) ;

R^2 is independently selected from:

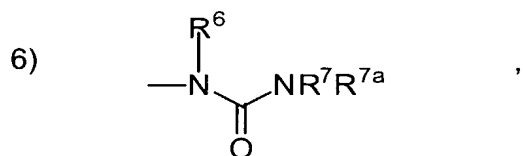
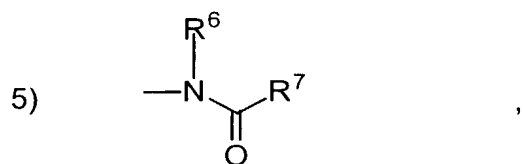
- a) hydrogen,
 b) CN,
 20 c) NO_2 ,
 d) halogen,
 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) C_1 - C_6 alkyl, unsubstituted or substituted,
 25 h) OR^{10} ,
 i) N_3 ,
 j) $\text{R}^{6a}\text{S(O)}_m$,
 k) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
 l) C_2 - C_6 alkenyl, unsubstituted or substituted,
 30 m) C_2 - C_6 alkynyl, unsubstituted or substituted,
 n) $(\text{R}^{10})_2\text{NC(O)NR}^{10}-$,
 o) $\text{R}^{10}\text{C(O)}-$,
 p) $\text{R}^{10}\text{C(O)NR}^{10}-$,
 q) $\text{R}^{10}\text{OC(O)}-$,

- r) $-\text{N}(\text{R}^{10})_2$,
- s) $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}$ -, and
- t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C}(\text{O})\text{R}^{13}$;

5 R^3 is independently selected from:
 H, CN, NO_2 , halo, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, N_3 , oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_6$
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 10 heterocyclylalkyl, $\text{C}_1\text{-C}_6$ perfluoroalkyl, $\text{CF}_3\text{O-}$, $\text{CF}_3\text{CH}_2\text{-}$, unsubstituted or
 substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, OR^{10} , NR^6R^7 , OR^6 , $-\text{C}(\text{O})\text{R}^{10}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$
 OR^{10} , $-\text{S}(\text{O})_m\text{R}^{6a}$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $-\text{NHC}(\text{O})\text{R}^{10}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{OR}^{10}$, and $-(\text{C}_1\text{-C}_6$
 $\text{alkyl})\text{C}(\text{O})\text{R}^{10}$;

15 R^4 and R^5 are independently selected from:
 H, OR^{10} , unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, wherein the substituted
 group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) $\text{C}_1\text{-C}_6$ alkyl,
 - 20 b) $(\text{CH}_2)_n\text{OR}^6$,
 - c) $(\text{CH}_2)_n\text{NR}^6\text{R}^7$,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - 25 g) perfluoro- $\text{C}_1\text{-C}_4$ alkyl,
 - h) $\text{S}(\text{O})_m\text{R}^{6a}$,
- 2) $\text{C}_3\text{-C}_6$ cycloalkyl,
- 3) OR^6 ,



8) halo, and

9) perfluoro- C_{1-4} -alkyl; or

5

R^4 and R^5 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , NR^{10} , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

10 and any of R^4 and R^5 are optionally attached to the same carbon atom;

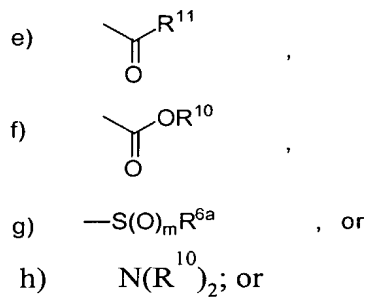
R^6 , R^7 and R^{7a} are independently selected from:

H, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, $\text{C}_1\text{—C}_4$ perfluoroalkyl, unsubstituted or

15 substituted with one or two substituents selected from:

- $\text{C}_1\text{—C}_6$ alkoxy,
- substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- halogen,
- HO,

20



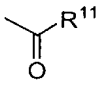
R^6 and R^7 may be joined in a ring;

5

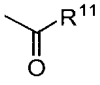
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted
 10 with one or more of the following:

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) HO,
- 5) ,
- 15 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of
 the following:

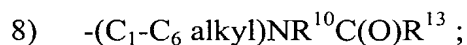
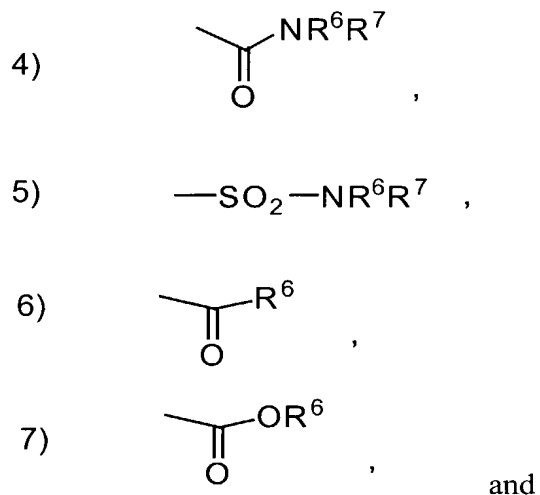
- 20 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) ,
- 25 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

- a) hydrogen, and
 b) C_1-C_6 alkyl, unsubstituted or substituted by C_1-C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{6a}S(O)_m-$, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2NC(O)NR^{10}-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}-$;

R^9 is independently selected from

- 1) H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- a) C_1-C_6 alkyl, unsubstituted or substituted,
 b) $(CH_2)_nOR^6$,
 c) $(CH_2)_nNR^6R^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1-C_4 alkyl,
 i) $S(O)_mR^{6a}$,
 j) $N(R^{10})_2$,
 k) $NR^{10}C(O)R^{11}$,
 l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 m) $-R^{10}(CH_2)_nR^{11}$,
- 2) C_3-C_6 cycloalkyl,
 3) $S(O)_mR^{6a}$,



5 R^{10} is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,
- c) $\text{C}_3\text{—C}_6$ cycloalkyl,
- d) 2,2,2-trifluoroethyl,
- 10 e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

15 R^{11} is independently selected from

- a) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted aryl, and
- 20 e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,

- 5 c) unsubstituted or substituted aryl,
 d) unsubstituted or substituted heterocycle,
 e) aralkyl, unsubstituted or substituted,
 f) heterocyclalkyl, unsubstituted or substituted,
 g) C₂-C₆ alkynyl, unsubstituted or substituted,
 h) C₂-C₆ alkenyl, unsubstituted or substituted,
 i) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
 j) CF₃,
 k) CF₃O-,
 10 l) CF₃CH₂-,
 m) OR¹⁰,
 n) -C(O)R¹⁰,
 o) -O(C₁-C₆ alkyl)OR¹⁰,
 p) -C(O)NR⁶R⁷,
 15 q) -(C₁-C₆ alkyl)OR¹⁰, and
 r) -(C₁-C₆ alkyl)C(O)R¹⁰;

G¹ is selected from oxygen or H₂;

- 20 Y is selected from
 a) C₁-C₈ alkyl,
 b) C₃-C₂₀ cycloalkyl,
 c) aryl, or
 d) heterocycle;

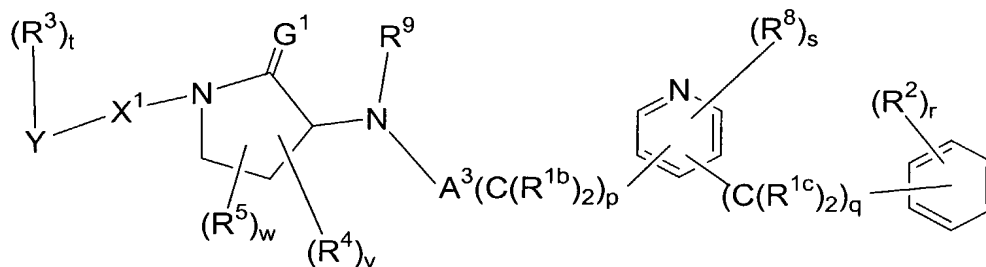
25

- m is 0, 1 or 2;
 n is 0, 1, 2, 3, 4, 5 or 6;
 p is 0, 1, 2, 3, or 4;
 q is 0, 1, 2, or 3;
 30 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and

w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

5 Another embodiment of the compounds of this invention is illustrated by formula E:



E

wherein

10 X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)(NR^{10})$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and
- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
 - b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted
- 5 aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^{6,7}$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

10

A^1 is selected from

- a) a bond,
- b) $-C(=O)-$,
- c) O,
- 15 d) NR^{10} ,
- e) $NR^{10}C(O)$,
- f) $C(O)NR^{10}$,
- g) $OC(O)NR^{10}$,
- h) $NR^{10}C(O)O$,
- 20 i) $S(=O)_m$,
- j) $C(O)O$, and
- k) $OC(O)$;

A^2 is selected from

- 25 a) a bond,
- b) $-C(=O)-$,
- c) $NR^{10}C(O)$, and
- d) $S(=O)_m$;

30 A^3 is selected from

- a) a bond, or
- b) $C(=O)$;

R^2 is independently selected from:

- a) hydrogen,
 b) CN,
 c) NO₂,
 d) halogen,
 5 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) C₁-C₆ alkyl, unsubstituted or substituted,
 h) OR¹⁰,
 i) N₃,
 10 j) R^{6a}S(O)_m,
 k) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
 l) C₂-C₆ alkenyl, unsubstituted or substituted,
 m) C₂-C₆ alkynyl, unsubstituted or substituted,
 n) (R¹⁰)₂NC(O)NR¹⁰-,
 15 o) R¹⁰C(O)-,
 p) R¹⁰C(O)NR¹⁰-,
 q) R¹⁰OC(O)-,
 r) -N(R¹⁰)₂,
 s) R¹⁰OC(O)NR¹⁰-, and
 20 t) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³;

R³ is independently selected from:

- H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 25 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclylalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰,
 30 and -(C₁-C₆ alkyl)C(O)R¹⁰;

R⁴ and R⁵ are independently selected from:

- H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, wherein the substituted
 group is substituted with one or more of:

- 5
- 1) aryl or heterocycle, unsubstituted or substituted with:
- C_1-C_6 alkyl,
 - $(CH_2)_nOR^6$,
 - $(CH_2)_nNR^6R^7$,
 - halogen,
 - CN,
 - aryl or heteroaryl,
 - perfluoro- C_1-C_4 alkyl,
 - $S(O)_mR^{6a}$,
- 10
- 2) C_3-C_6 cycloalkyl,
- 3) OR^6 ,
- 4) $—NR^6R^7$,
- 5) $\begin{array}{c} R^6 \\ | \\ —N—C(=O)—R^7 \end{array}$,
- 6) $\begin{array}{c} R^6 \\ | \\ —N—C(=O)—NR^7R^{7a} \end{array}$,
- 7) $\begin{array}{c} R^6 \\ | \\ —C(=O)— \end{array}$,
- 8) halo, and
- 15
- 9) perfluoro- C_{1-4} -alkyl; or

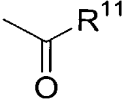
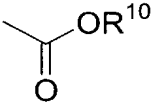
R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, NR^{10} , $-NC(O)-$, and $-N(COR^{10})-$;

20

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

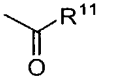
H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1 - C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

- 5 a) C_1 - C_6 alkoxy,
 b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
 c) halogen,
 d) HO,
 e) ,
 f) ,
 g) $-S(O)_m R^{6a}$, or
 h) $N(R^{10})_2$; or
- 10

R^6 and R^7 may be joined in a ring;

- 15 R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

- a) C_3 - C_6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted
- 20 with one or more of the following:
- 1) C_{1-4} alkoxy,
 2) aryl or heterocycle,
 3) halogen,
 4) HO,
 5) ,
 6) $SO_2 R^{6a}$,
 7) $N(R^{10})_2$; and
- 25

b) C₁-C₆ alkyl, unsubstituted or substituted with one or more of the following:

- 1) -C(R¹⁰)₂C₁₋₄ alkoxy,
- 2) aryl or heterocycle,
- 3) -C(R¹⁰)₂halogen,
- 4) -C(R¹⁰)₂OH,
- 5) $\begin{array}{c} \text{R}^{11} \\ \diagup \\ \text{C} \\ \parallel \\ \text{O} \end{array}$,
- 6) -C(R¹⁰)₂SO₂R^{6a}, and
- 7) -C(R¹⁰)₂N(R¹⁰)₂;

10

R⁸ is independently selected from

- a) hydrogen, and
- b) C₁-C₆ alkyl, unsubstituted or substituted by C₁-C₄ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R^{6a}S(O)_m-, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃-, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

15

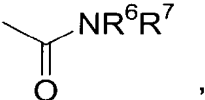
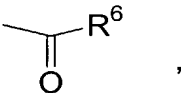
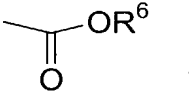
R⁹ is independently selected from

- 1) H, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₈ alkenyl, unsubstituted or substituted C₂-C₈ alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
 - a) C₁-C₆ alkyl, unsubstituted or substituted,
 - b) (CH₂)_nOR⁶,
 - c) (CH₂)_nNR⁶R⁷,
 - d) halogen,
 - e) CN,
 - f) aryl, unsubstituted or substituted,
 - g) heterocycle, unsubstituted or substituted,
 - h) perfluoro-C₁-C₄ alkyl,
 - i) S(O)_mR^{6a},
 - j) N(R¹⁰)₂,

20

25

30

- 5
- k) $\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$,
 l) $\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}\text{N}(\text{R}^{10})_2$,
 m) $-\text{R}^{10}(\text{CH}_2)_n\text{R}^{11}$,
 2) $\text{C}_3\text{-C}_6$ cycloalkyl,
 3) $\text{S}(\text{O})_m\text{R}^{6a}$,
 4) ,
 5) $-\text{SO}_2-\text{NR}^6\text{R}^7$,
 6) ,
 7) , and
 8) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C}(\text{O})\text{R}^{13}$;

10 R^{10} is independently selected from

- a) hydrogen,
 b) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
 c) $\text{C}_3\text{-C}_6$ cycloalkyl,
 d) 2,2,2-trifluoroethyl,
 15 e) unsubstituted or substituted heteroaryl,
 f) unsubstituted or substituted aryl,
 g) unsubstituted or substituted aralkyl, and
 h) unsubstituted or substituted heterocyclalkyl;

20 R^{11} is independently selected from

- a) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
 b) unsubstituted or substituted aralkyl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted aryl, and

- e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- 5 a) H,
 b) unsubstituted or substituted C_1-C_6 alkyl,
 c) unsubstituted or substituted aryl,
 d) unsubstituted or substituted heterocycle,
 e) aralkyl, unsubstituted or substituted,
 10 f) heterocyclalkyl, unsubstituted or substituted,
 g) C_2-C_6 alkynyl, unsubstituted or substituted,
 h) C_2-C_6 alkenyl, unsubstituted or substituted,
 i) C_3-C_{10} cycloalkyl, unsubstituted or substituted,
 j) CF_3 ,
 15 k) CF_3O- ,
 l) CF_3CH_2- ,
 m) OR^{10} ,
 n) $-C(O)R^{10}$,
 o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
 20 p) $-C(O)NR^6R^7$,
 q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 is selected from oxygen or H_2 ;

25

Y is selected from

- a) C_1-C_8 alkyl,
 b) C_3-C_{20} cycloalkyl,
 c) aryl, or
 30 d) heterocycle;

m is 0, 1 or 2;

n is 0, 1, 2, 3, 4, 5 or 6;

p is 0, 1, 2, 3, or 4;

- q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4;
 5 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

10

Specific examples of the compounds of the invention are:

(*R*)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

- 15 (*S*)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

(*R*)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

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(*S*)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

- 25 (*R*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl) benzonitrile,

(*S*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

- 30 (*R*)-4-(5-{[1-(3-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{[1-(3-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

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- (*R*)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 5 (*S*)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[1-(2-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 10 (*S*)-4-(5-{[1-(2-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 15 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[1-(4-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 20 (*S*)-4-(5-{[1-(4-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 25 (*R*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,
- (*S*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,
- 30 (*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)acetamide,
- (*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)acetamide,
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- (*R*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl] acetamide,
- 5 (*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl] acetamide,
- (*R*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-methylacetamide,
- 10 (*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-methylacetamide,
- (*R*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- 15 (*S*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- (*R*)-4-(5-{[Benzyl(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 20 (*S*)-4-(5-{[Benzyl(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)phenethylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 25 (*S*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)phenethylamino]methyl}imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)(3-phenylpropyl)amino]methyl}imidazol-1-ylmethyl)benzonitrile,
- 30 (*S*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)(3-phenylpropyl)amino]methyl}imidazol-1-ylmethyl)benzonitrile,
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(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)(4-phenylbutyl)amino}methyl}imidazol-1-ylmethyl)benzonitrile,

5 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)(4-phenylbutyl)amino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino}methyl}imidazol-1-ylmethyl) benzonitrile,

10 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino}methyl}imidazol-1-ylmethyl) benzonitrile,

(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino}methyl}imidazol-1-ylmethyl) benzonitrile,

15 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino}methyl}imidazol-1-ylmethyl) benzonitrile,

20 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-2-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-2-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

25 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-3-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-3-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

30 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-4-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

35 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-4-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

5 (*S*)-4-(5-{[(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[(2-Aminoethyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

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(*S*)-4-(5-{[(2-Aminoethyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[(4-Aminobutyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

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(*S*)-4-(5-{[(4-Aminobutyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl} imidazol-1-ylmethyl)benzonitrile,

20 (*R*)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,

(*S*)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,

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(*R*)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,

(*S*)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}

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benzonitrile,

(*R*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,

- (*S*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- (*R*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[1-(Naphthalene-2-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(Naphthalene-2-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- (*S*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- (*R*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide,
- (*S*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide,
- (*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-[1-(naphthalene-1-carbonyl)pyrrolidin-3-yl]acetamide,
- (*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-[1-(naphthalene-1-carbonyl)pyrrolidin-3-yl]acetamide,
- (*R*)-4-(5-{[1-(3-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl) benzonitrile,
- (*S*)-4-(5-{[1-(3-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl) benzonitrile,

- (*R*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- (*S*)-4-(5-{[1-(2-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl) benzonitrile,
- 5 (*R*)-4-(5-{[1-(2-Methylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(2-Methylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 10 (*R*)-4-(5-{[1-(Isoquinoline-4-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(Isoquinoline-4-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 15 (*R*)-4-(5-{[1-(5-Bromopyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(5-Bromopyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 20 (*R*)-4-(5-{[1-(2-Methylsulfanylpiperidine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 25 (*S*)-4-(5-{[1-(2-Methylsulfanylpiperidine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{[1-(2-Ethylsulfanylpiperidine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 30 (*S*)-4-(5-{[1-(2-Ethylsulfanylpiperidine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
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- 4-(5-{{(3*R*)-1-(*trans*-Cotinine-4-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 5 4-(5-{{(3*S*)-1-(*trans*-Cotinine-4-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(Biphenyl-2-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 10 (*S*)-4-(5-{{1-(Biphenyl-2-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 15 (*S*)-4-(5-{{1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenoxybenzonitrile,
- 20 (*S*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenoxybenzonitrile,
- 25 (*R*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile,
- (*S*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile,
- 30 (*R*)-2-Benzyloxy-4-(5-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 35 (*S*)-2-Benzyloxy-4-(5-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,

- (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile,
- 5 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile,
- (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile,
- 10 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile,
- (*R*)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,
- 15 (*S*)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,
- (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](3-phenylpropyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 20 (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](3-phenylpropyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 25 (*R*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 30 (*R*)-*N*-(3-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,

- (*S*)-*N*-(3-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- 5 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 10 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 15 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][2-(pyridin-2-ylamino) ethyl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][2-(pyridin-2-ylamino) ethyl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 20 (*R*)-6-Amino-*N*-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- 25 (*S*)-6-Amino-*N*-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- (3*S*)-4-[5-({1-[(*S*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- 30 (3*S*)-4-[5-({1-[(*R*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- (3*R*)-4-[5-({1-[(*R*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
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- (3*R*)-4-[5-({1-[(*S*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- 5 (3*S*)-2-Fluoro-4-[5-({1-[(*S*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- (3*S*)-2-Fluoro-4-[5-({1-[(*R*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- 10 (3*R*)-2-Fluoro-4-[5-({1-[(*R*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- (3*R*)-2-Fluoro-4-[5-({1-[(*S*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- 15 (3*R*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- (*R*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- 20 (*S*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- (*R*)-2-Fluoro-4-[1-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-yl)eth-1-yl]benzonitrile,
- 25 (*S*)-2-Fluoro-4-[1-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-yl)eth-1-yl]benzonitrile,
- (*R*)-3- { [1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino } pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide,
- 30 (*S*)-3- { [1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino } pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide,

(*R*)-3- {[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (2,6-difluorophenyl)amide,

5 (*S*)-3- {[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (2,6-difluorophenyl)amide,

(*R*)-4-(5- {[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile,

10 (*S*)-4-(5- {[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile,

(*R*)-4- {5-[(2-Oxo-1-pyridin-4-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

15 (*S*)-4- {5-[(2-Oxo-1-pyridin-4-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

(*R*)-4- {5-[(2-Oxo-1-pyridin-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

(*S*)-4- {5-[(2-Oxo-1-pyridin-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

25 (*R*)-4- {5-[(2-Oxo-1-pyrazin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

(*S*)-4- {5-[(2-Oxo-1-pyrazin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

30 (*R*)-4- {5-[(2-Oxo-1-tetrahydrofuran-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

(*S*)-4- {5-[(2-Oxo-1-tetrahydrofuran-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;

35

- (*R*)-4-{5-[(2-Oxo-1-thiazol-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 5 (*S*)-4-{5-[(2-Oxo-1-thiazol-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(1-(4-Morpholinophenyl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 10 (*S*)-4-{5-[(1-(4-Morpholinophenyl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(1-(1-Benzylpyrrolidin-3-yl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 15 (*S*)-4-{5-[(1-(1-Benzylpyrrolidin-3-yl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(2-Oxo-1-quinolin-5-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 20 (*S*)-4-{5-[(2-Oxo-1-quinolin-5-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 25 (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl})imidazol-1-ylmethyl} benzonitrile;
- (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl})imidazol-1-ylmethyl} benzonitrile;
- 30 (*S*)-4-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole;
- 35 (*R*)-4-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-

(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole,;

(*R*)-2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile;

5

(*S*)-2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile;

(*R*)-4-(5-{[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]ethyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile;

10

(*S*)-4-(5-{[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]ethyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile;

15

(*R*)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine;

(*S*)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine;

20

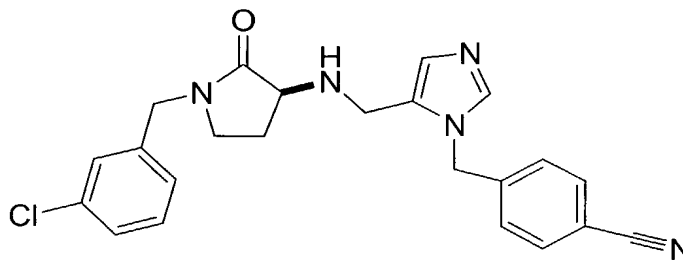
(*R*)-3-{[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine;

(*S*)-3-{[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine;

25

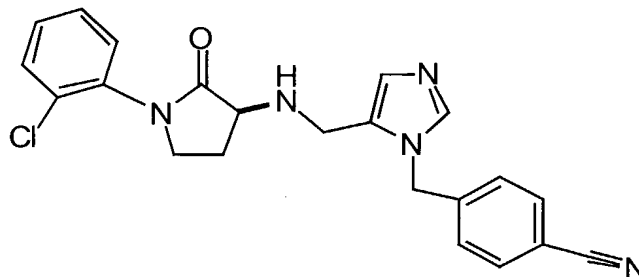
or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

Specific examples of compounds of the instant invention are

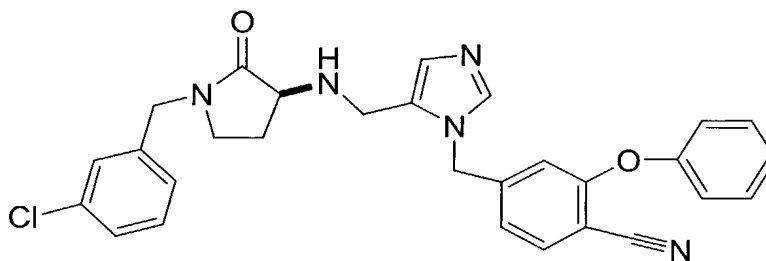


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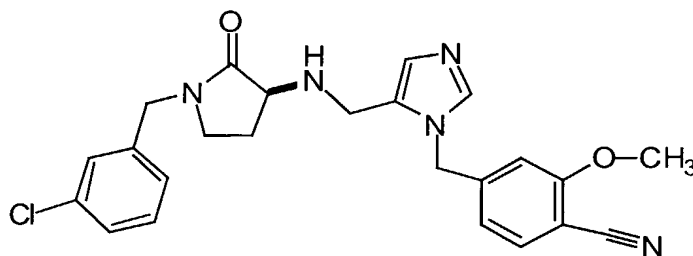
(*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,



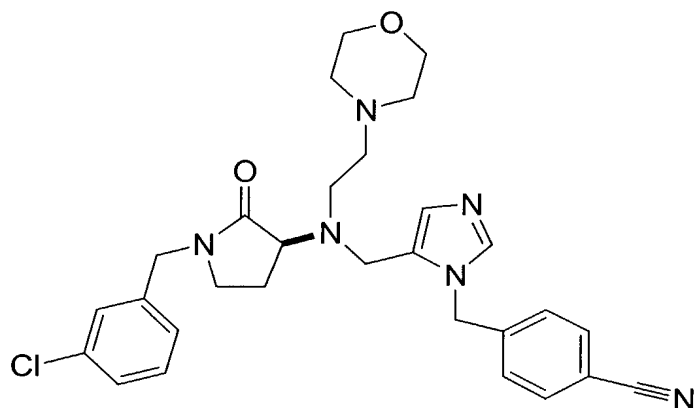
5 (*S*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,



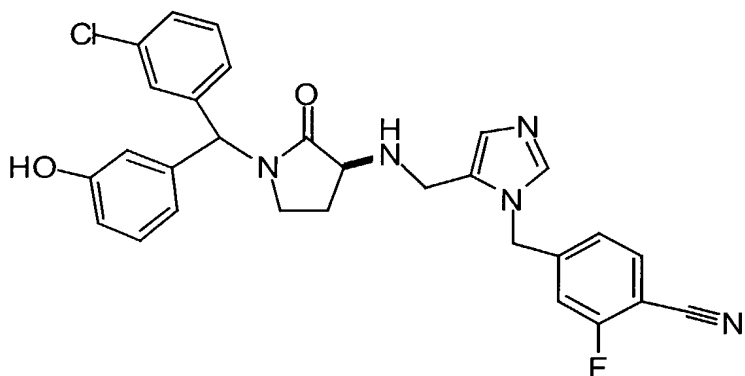
10 (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenoxybenzonitrile,



15 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile,

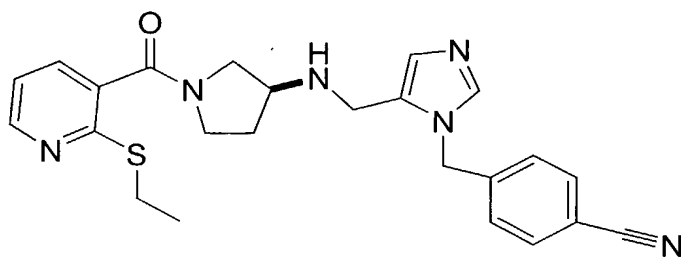


(*S*)-4-[5-({1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl}(2-morpholin-4-ylethyl)amino)methyl]imidazol-1-ylmethyl]benzonitrile,



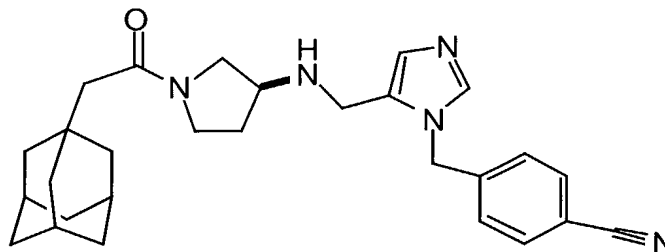
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(*3S*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-yl}amino)methyl]imidazol-1-ylmethyl]-2-fluorobenzonitrile,



10

4-(5-({[(*3S*)-1-(2-Ethylsulfanylpent-3-en-2-yl)pyridine-3-carbonyl]pyrrolidin-3-yl}amino)methyl)imidazol-1-ylmethyl]benzonitrile,



(*S*)-4-(5-{[1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile

5 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present
 10 invention. When any variable, term or substituent (e.g. aryl, heterocycle, n, R^{1a}, etc.) occurs more than one time in any formula or generic structure, its definition on each occurrence is independent from the definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

15 As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having 1 to 6 carbon atoms, unless otherwise specified; "alkoxy" represents an alkyl group having 1 to 6 carbon atoms, unless otherwise indicated, attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo. "Cycloalkyl" as used
 20 herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, and the like.

25 If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical having from

2 to 6 carbon atoms. Examples of such alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

5 The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Examples of such alkynyl groups include, but are not limited to, ethynyl, propynyl and butynyl. As described
10 above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

 As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one
15 ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralinyl, tetralonyl, fluorenyl, phenanthryl, anthryl or acenaphthyl.

 As used herein, "aralkyl" is intended to mean an aryl moiety, as defined above, attached through a C₁-C₆ alkyl linker, where alkyl is defined above.
20 Examples of aralkyls include, but are not limited to, benzyl, naphthylmethyl and phenylbutyl.

 The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of
25 carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl,
30 benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzopyrazolyl, benzotriazolyl, chromanyl, cinnolinyl, dibenzofuranyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydroimidazothiazolyl, furyl, furanyl, imidazolidinyl, imidazolyl, imidazolyl,
35 indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl,

isothiazolyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 4-oxonaphthyridinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, 2-oxopyridyl, 2-oxoquinolinyl, piperidyl, piperazinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuranyl, tetrahydrofuryl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heteroaryl elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofuranyl, benzofurazanyl, benzopyranyl, benzopyrazolyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzotriazolyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furanyl, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroimidazopyridinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, thienyl and triazolyl.

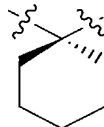
As used herein, "heterocyclalkyl" is intended to mean a heterocyclic moiety, as defined above, attached through a C₁-C₆ alkyl linker, where alkyl is defined above. Examples of heterocyclalkyls include, but are not limited to, 2-pyridylmethyl, 2-morpholinylethyl, 2-imidazolylethyl, 2-quinolinylmethyl, 2-imidazolylmethyl, 1-piperazineethyl, and the like.

As used herein, the terms "substituted alkyl", "substituted alkenyl", "substituted alkynyl" and "substituted alkoxy" are intended to include the branch or straight-chain alkyl group of the specified number of carbon atoms, wherein the carbon atoms may be substituted with F, Cl, Br, I, CF₃, N₃, NO₂, NH₂, oxo, OH, -O(C₁-C₆ alkyl), S(O)_{0.2}, (C₁-C₆ alkyl)S(O)_{0.2}, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -(C₁-C₆ alkyl)S(O)_{0.2}(C₁-C₆ alkyl), C₃-C₂₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C(O)NH, (C₁-C₆ alkyl)C(O)NH-, H₂N-CH(NH)-, (C₁-C₆ alkyl)C(O)-, -O(C₁-C₆ alkyl)CF₃,

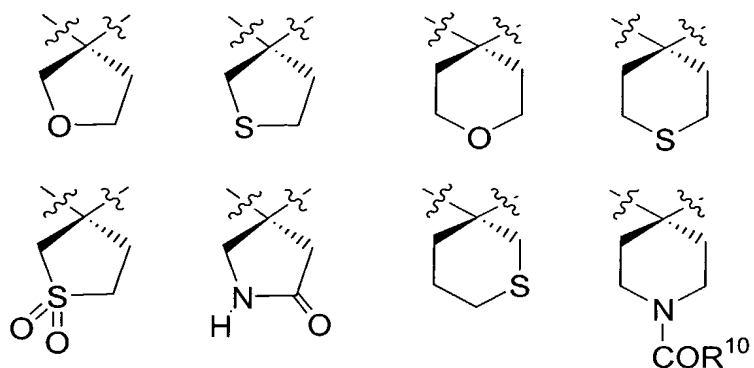
(C₁-C₆ alkyl)OC(O)-, (C₁-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)C(O)₂(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)OC(O)NH-, aryl, benzyl, heterocycle, aralkyl, heterocyclylalkyl, halo-aryl, halo-benzyl, halo-heterocycle, cyano-aryl, cyano-benzyl and cyano-heterocycle.

- As used herein, the terms “substituted aryl”, “substituted heterocycle”, “substituted heteroaryl”, “substituted cycloalkyl”, “substituted benzyl”, “substituted aralkyl” and “substituted heterocyclylalkyl” are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Such substituents are preferably selected from the group which includes but is not limited to F, Cl, Br, I, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, N₃, C₁-C₂₀ alkyl, C₁-C₆ alkoxy, C₃-C₂₀ cycloalkyl, -OH, -O(C₁-C₆ alkyl), S(O)_{0.2}, (C₁-C₆ alkyl)S(O)_{0.2}-, (C₁-C₆ alkyl)S(O)_{0.2}(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)C(O)NH-, H₂N-CH(NH)-, H₂N-C(O)NH-(C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, (C₁-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₁-C₆)C(O)₂(C₁-C₆ alkyl)-, (C₁-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

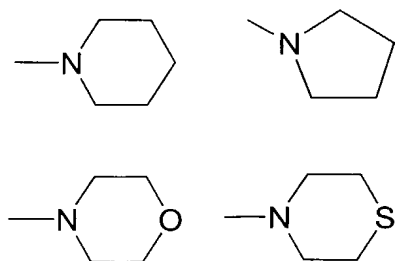
When R⁴ and R⁵ are combined to form -(CH₂)_u-, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:



- In addition, with respect to R⁴ and R⁵, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:

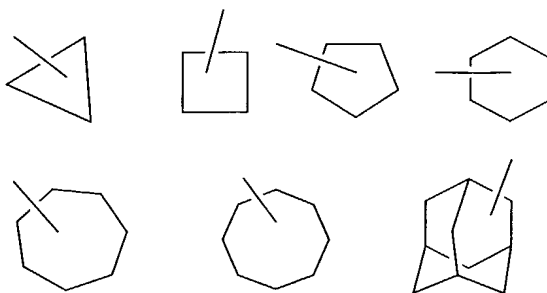


Examples of the ring structures which may be formed when R^6 and R^7 , or R^7 and R^{7a} , are joined include, but are not limited to,



5

As used herein, examples of "C₃ - C₂₀ cycloalkyl" may include, but are not limited to:



Lines drawn into the ring systems from substituents (such as from R^4 , R^5 , X^1 , etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms or heteroatoms.

10

Preferably, R^2 is independently selected from hydrogen, $-OR^{10}$, CN, unsubstituted or substituted aryl and halogen. Most preferably, r is 1 to 3 and at least one R^2 is CN.

5 Preferably, R^3 is independently selected from hydrogen, halo, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, $-NR^6R^7$, oxido, $-S(O)_mR^{6a}$, $-OR^{10}$, and C_1-C_6 perfluoroalkyl.

10 Preferably, R^4 and R^5 are independently selected from hydrogen, unsubstituted or substituted C_1-C_6 alkyl, OR^{10} . Most preferably, R^4 and R^5 are independently selected from hydrogen or unsubstituted or substituted C_1-C_6 alkyl.

Preferably, R^8 is selected from hydrogen, or unsubstituted or substituted C_1-C_6 alkyl. Most preferably, R^8 is selected from hydrogen or methyl.

Preferably, R^9 is selected from hydrogen, unsubstituted or substituted C_1-C_6 alkyl, and unsubstituted or substituted aryl.

15 Preferably, R^{10} is selected from hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl, or unsubstituted or substituted heterocycle.

Preferably, X^2 is selected from $C(O)(CH_2)_p$ or $(CH_2)_p$, where p is 1 or 2.

Preferably, X^3 is $(CR^{1b})_p$, where p is 1 or 2.

20 Preferably, A^1 is selected from a bond, $C(O)$, $-NR^{10}C(O)-$, $OC(O)NR^{10}$ or $S(O)_m$.

Preferably, A^2 is selected from a bond, $-NR^{10}C(O)-$, $C(O)$, or $S(O)_m$.

Preferably, A^3 is selected from a bond, $C(O)$, or $S(O)_m$.

Preferably, A^4 is a bond or $C(O)$. Most preferably, A^4 is a bond.

25 Preferably, G^2 is H_2 .

Preferably, V is selected from aryl or heterocycle. More preferably, V is aryl. Most preferably, V is phenyl.

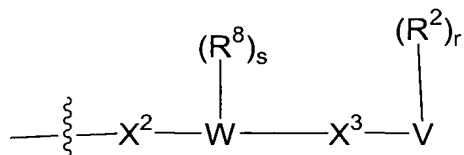
30 Preferably, W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, 2-oxopiperidinyl, quinolinyl, isoquinolinyl, and thienyl. More preferably, W is imidazolyl or pyridinyl. Most preferably, W is imidazolyl.

Preferably, Y is selected from aryl, heterocycle, C_1-C_6 alkyl or a C_3-C_{10} cycloalkyl. More preferably, Y is aryl or heterocycle.

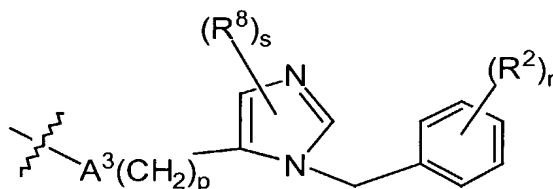
Preferably, n , p , and q are independently 0, 1, 2, 3 or 4.

Preferably, r , s and t are independently selected from 0, 1, 2, or 3.

Preferably, the moiety

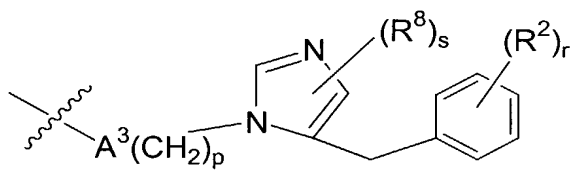


represents



5

or



where p is 1 or 2.

It is intended that the definition of any substituent or variable (e.g., R^{1a} , R^2 , m, p, etc.) at a particular location in a molecule is independent of its definitions elsewhere in that molecule. Thus, $-\text{C}(\text{R}^{1a})_2$ can represent $-\text{CH}_2$, $-\text{CHCH}_3$, $-\text{CHC}_2\text{H}_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as

hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Abbreviations which may be used in the description of the chemistry and in the Examples that follow include:

| | | |
|----|-------------------|---|
| 15 | Ac ₂ O | Acetic anhydride; |
| | AIBN | 2,2'-Azobisisobutyronitrile |
| | BOC/Boc | t-Butoxycarbonyl or <i>tert</i> -butoxycarbonyl; |
| | CBz | Carbobenzyloxy; |
| | DBAD | Di- <i>tert</i> -butyl azodicarboxylate; |
| 20 | DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene; |
| | DCE | 1,2-Dichloroethane; |
| | DIEA | <i>N,N</i> -Diisopropylethylamine; |
| | DMAP | 4-Dimethylaminopyridine; |
| | DME | 1,2-Dimethoxyethane; |
| 25 | DMF | <i>N,N</i> -Dimethylformamide; |
| | DMSO | Methyl sulfoxide; |
| | DPPA | Diphenylphosphoryl azide; |
| | DTT | Dithiothreitol; |
| | EDC | 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride; |
| 30 | EDTA | Ethylenediaminetetraacetic acid; |
| | Et ₃ N | Triethylamine; |
| | EtOAc | Ethyl acetate; |
| | EtOH | Ethanol; |
| | FAB | Fast atom bombardment; |
| 35 | HEPES | 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid; |

| | | |
|----|---------------------|--|
| | HOBt | 1-Hydroxybenzotriazole hydrate; |
| | HOObt | 3-Hydroxy-1,2,2-benzotriazin-4(3 <i>H</i>)-one; |
| | HPLC | High-performance liquid chromatography; |
| | LAH | Lithium aluminum hydride; |
| 5 | MCPBA | <i>m</i> -Chloroperoxybenzoic acid; |
| | Me | Methyl; |
| | MeOH | Methanol; |
| | Ms | Methanesulfonyl; |
| | MsCl | Methanesulfonyl chloride; |
| 10 | n-Bu ₃ P | Tri- <i>n</i> -butylphosphine; |
| | NaHMDS | Sodium bis(trimethylsilyl)amide; |
| | NBS | <i>N</i> -Bromosuccinimide; |
| | PMSF | <i>a</i> -Toluenesulfonyl chloride; |
| | Py or pyr | Pyridine; |
| 15 | PYBOP | Benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate; |
| | <i>t</i> -Bu | <i>tert</i> -Butyl |
| | TBAF | Tetrabutylammoniumfluoride |
| | RPLC | Reverse Phase Liquid Chromatography |
| 20 | TBSCl | <i>tert</i> -Butyldimethylsilyl chloride |
| | TFA | Trifluoroacetic acid; |
| | THF | Tetrahydrofuran; |
| | TMS | Tetramethylsilane; |
| | Tr | Trityl; |

25

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The procedures discussed and illustrated in the following schemes and synopsis may be used in the preparation of the compounds of the instant invention, for either (*R*) or (*S*) stereochemistry.

30

Synopsis of Schemes

35

Unless otherwise indicated, variable *n* is defined as 0 to 6 and variable *p* is defined as 0 to 4.

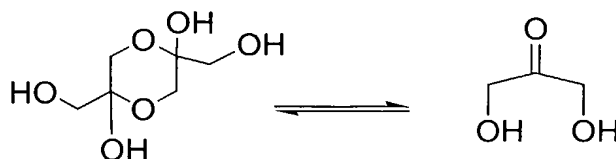
Scheme 1 depicts the synthesis of intermediate amide **1**. One variation starts with the EDC-mediated coupling of methionine with the amine of interest to give amide **1**. A second variation of this procedure uses PYBOP and DIEA in dichloromethane to achieve the initial coupling of the amine and methionine.

5 Scheme 2 details the construction of various 1-substituted 3-amino-pyrrolidinones. Amide **1** is treated with excess iodomethane, and the resulting sulfonium salt undergoes cyclization upon reaction with lithium Bis(trimethylsilyl) amide in THF at 0°C to give the simple pyrrolidinone **2**. Treatment of compound **2** with lithium bis(trimethyl-silyl)amide in THF at 0°C, followed by iodomethane, provides the methylated analog **3**.

10 Scheme 3 demonstrates the synthesis of suitably substituted imidazolyl acetic acids. Thus, the imidazole acetic acid **4** can be converted to the ester **5** by standard procedures. Selective nitrogen protection provides intermediate **6** which is first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **7**. The ester **7** can be converted to the acetic acid **8** using either aqueous HCl or LiOH.

 Scheme 3A illustrates the synthesis of aldehyde **A** using the imidazolyl alcohol **9**. Treating the imidazolyl alcohol **9** with triethyl-amine and tritylchloride in DMF yielded the protected imidazolyl alcohol **10**. This alcohol **10** can be converted to the TBS ether intermediate **B** using TBSCl in DIEA, CH₂Cl₂ and DMAP. Treating the alcohol **10** with pyridine and acetic anhydride will also yield the ester **11**. Using a substituted benzylbromide, ethyl acetate and then methanol, the ester **11** is converted to the benzylimidazolyl ester **12**. Treating **12** with LiOH will yield the benzyl-imidazolyl alcohol **13** which can be converted to aldehyde **A** using triethylamine and SO₃-Py in DMSO

25 Scheme 3B demonstrates an alternative route for the synthesis of aldehyde **A**. Benzyl bromide **14** is treated with hexamethyenetetramine in ethanol, resulting in compound **15**. Compound **15** is then treated with H₃PO₄, ethanol, and propionic acid to convert compound **15** to the benzylamine phosphate salt **16**. The phosphate salt is converted to the imidazolyl **17**, using DHA, KSCN, C₂H₅COOH in MeCN and water. DHA represents dihydroxyacetone and its dimer in equilibrium, as shown below:



Using hydrogen peroxide, HOAc and water, **17** is converted to benzylimidazolyl alcohol **18**. The benzylimidazolyl alcohol **18** is then converted to aldehyde **A** using triethylamine and SO₃-Py in DMSO.

The BOC-protected 3-aminopyrrolidinone of general structure **2** can be deprotected, as depicted in Scheme 4, with HCl in EtOAc at 0°C to give the corresponding amine **19**. As shown, this amine **19** is then reductively alkylated with aldehyde **A** using either NaCNBH₃ in methanol, or NaBH(OAc)₃ in 1,2-dichloroethane, to provide the secondary amine **20**. Similarly, compound **21** in Scheme 5 may be converted to compound **23** by analogous procedures.

Scheme 5A demonstrates the synthesis of an isomeric pyrrolidinone. The synthesis of the 3-aminopyrrolidinone **19a** begins by treating the amine and a BOC-protected aspartic acid ethyl ester with PYBOP and DIEA. The resulting product is treated with Lawesson's reagent and the desired aminopyrrolidinone is cyclized using NaBH₄ and NiCl₂ to obtain the intermediate **5**. Using techniques described above, the intermediate **2a** is converted to the compound **19a**, which may be used as a substitute for the basic 3-aminopyrrolidinone in any of the following schemes.

Scheme 6 shows the synthesis of amides of structure **24**. As before, deprotection of the amine functionality in **21** gives **22**, which is then coupled to the carboxylic acid, such as described in Scheme 3, using EDC, HOBT and DIEA in DMF. Application of these same procedures to the *N*-methyl carbamate **3** (from Scheme 2) produces the tertiary amide **26** in Scheme 7.

The synthesis of two useful aldehydes is detailed in Scheme 8. Firstly, an aminoalcohol is protected with a BOC group by treatment with di-*tert*-butyl dicarbonate and DIEA in DMF, and the resulting alcohol is subjected to standard Swern oxidation conditions to give aldehyde **28**. In the second case, ethylene glycol is selectively monoprotected by reaction of its sodium alkoxide with *tert*-butyldimethylsilyl chloride in THF. Swern oxidation of the monoprotected alcohol gives the desired aldehyde **29**.

Compound **23** (from Scheme 5) may be reductively alkylated with aldehyde **28** and NaCNBH₃ in methanol to give the tertiary amine derivative **30**, as shown in Scheme 9. Deprotection of **30** with HCl in EtOAc affords the amine **31**. Aldehyde **29** may be employed in a similar series of reactions to provide the
5 corresponding hydroxyl compound of the instant invention.

Reductive alkylation of compound **23** with aldehyde **29** using NaCNBH₃ in methanol, provides structure **32** in Scheme 10. This silyl ether is deprotected by treatment with TBAF in THF, and the resulting alcohol **33** is subjected to standard Swern oxidation to provide aldehyde **34**. This aldehyde
10 **34** can be reductively aminated with, for example, morpholine under standard NaCNBH₃ conditions to afford the instant compound **35**.

Scheme 11 demonstrates a route to imidazolylethyl derivatives such as **38**. The methyl ester **7A** is converted to the alcohol **36** using NaBH₄ and methanol. Then the alcohol **36** is converted to the corresponding mesylate **37** using methane-
15 sulfonyl chloride and DIEA in dichloromethane. Reaction of aminopyrrolidinone **22** with a mixture of this mesylate, sodium iodide, and DIEA in DMF at 50°C affords compound **38**.

In Scheme 12, 3-(trifluoroacetamido)pyrrolidine is treated with di-*tert*-butyl dicarbonate and DIEA in dichloromethane, and the resulting carbamate
20 is treated with lithium hydroxide in aqueous THF to provide the protected aminopyrrolidine **39**.

Reductive alkylation of amine **39** with aldehyde **A** is carried out using standard NaCNBH₃ conditions to give compound **40** in Scheme 13. Removal of the BOC group using HCl in EtOAc, followed by EDC coupling of the amine with
25 carboxylic acid (R^aCO₂H) provides the amide derivative **41**.

Scheme 13A illustrates the synthesis of compound **41a**, where compound **40** is deprotected, then reacted with the isocyanate (in THF) to provide the desired urea.

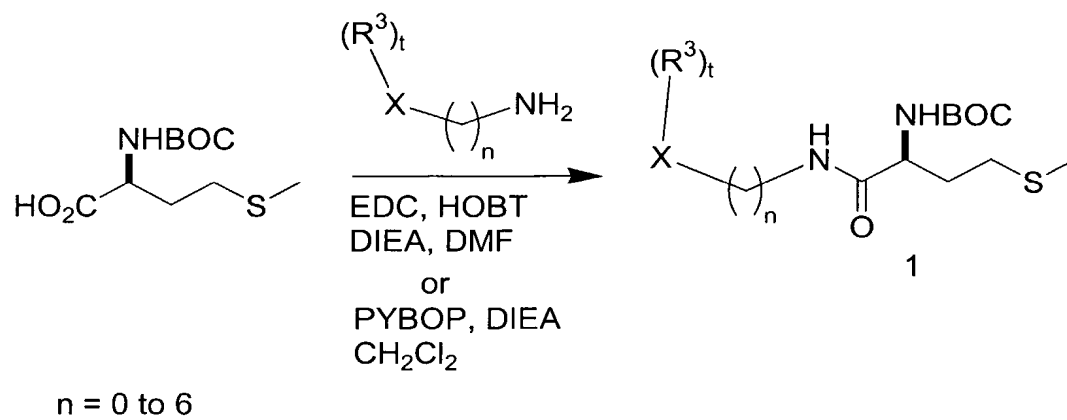
The aryl fluoride **42**, prepared as illustrated in Scheme 4 but using
30 a suitably substituted fluorobenzyl imidazolyl aldehyde, may be converted to the corresponding aryl ethers **43** and **44** as shown in Scheme 14. For aliphatic alcohols (R^bOH), it is preferable to use potassium *tert*-butoxide as the base in THF at low temperature, and this yields compound **43**. In the case of reaction with a phenol (R^aOH), use of cesium carbonate as base in DMF at 40°C affords the instant ether **44**.

Scheme 15 illustrates the synthesis of a 3-amino-1-pyridin-2-ylpyrrolidinone **50**. In this case, BOC-protected homoserine lactone is treated with the dimethylaluminum amide of the appropriate aminopyridine **46**. The resulting homoserine derivative **47** is reacted with di-*tert*-butyl azodicarboxylate and tributylphosphine in THF to afford the pyrrolidinone **48**. The standard deprotection and reductive amination procedures yield the instant compound **50**.

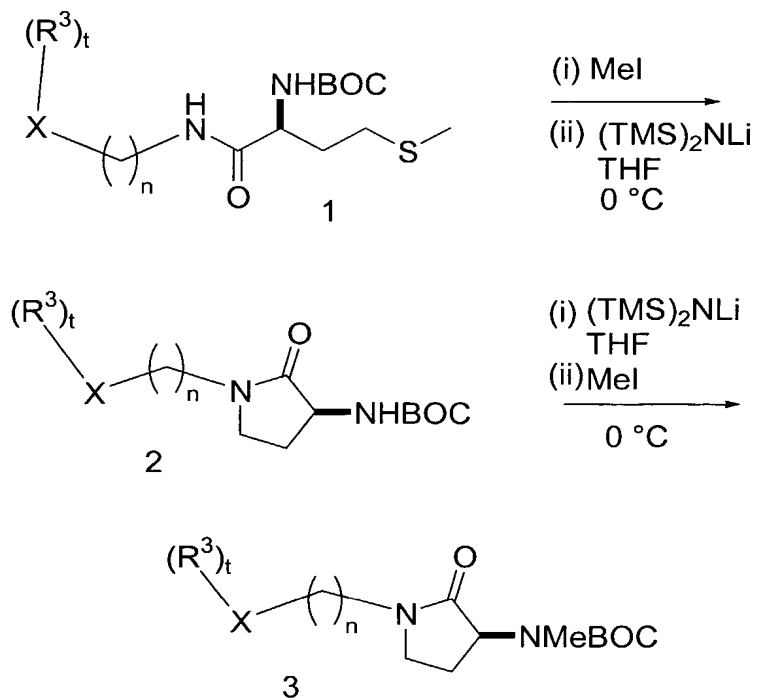
The synthesis of 1-(diarylmethyl)pyrrolidinone intermediates such as **57** is illustrated in Scheme 16. Benzyl 3-bromophenyl ether **51** is treated with magnesium in THF, and the resulting Grignard reagent is reacted with 3-chlorobenzaldehyde to give the alcohol **52**. This alcohol can be converted to the corresponding azide **53** using DPPA and DBU in toluene, and reduction of the azide by treatment with LAH in THF affords the amine **54**. Coupling of amine **54** and methionine is effected by treatment with PYBOP and DIEA in dichloromethane to give amide **55** as a mixture of diastereomers. This amide **55** is treated with excess iodomethane, and the resulting sulfonium salt undergoes cyclization upon reaction with lithium bis(trimethylsilyl)amide in THF at 0°C to give the pyrrolidinone **56**. The benzyl ether can be removed by hydrogenolysis over Pd(OH)₂ in ethanol and acetic acid to give phenol **57**, and the diastereomers may be separated by chromatography on silica gel, as shown in Scheme 17. A pure diastereomer, for example structure **58** in Scheme 17, is treated with HCl in EtOAc at 0°C to give the amine **59**, and this is subjected to reductive alkylation with aldehyde **A** and NaCNBH₃ in methanol to provide compound **60**.

In Scheme 18, benzaldehyde **61** is treated with methyl-magnesium bromide in THF at -78°C to give the alcohol **62**. A mixture of this alcohol, intermediate **B** (as described in Scheme 3A) and DIEA in dichloromethane at -78°C is treated with trifluoromethanesulfonic anhydride, and the resulting imidazolium salt is heated in methanol to provide the imidazole **64**. The silyl ether is deprotected using TBAF in THF and the resulting alcohol is converted to the aldehyde **65** by treatment with sulfur trioxide-pyridine complex and triethylamine in DMSO. This aldehyde can be reacted with amine **19** and NaCNBH₃ in methanol to provide the desired compound **66**.

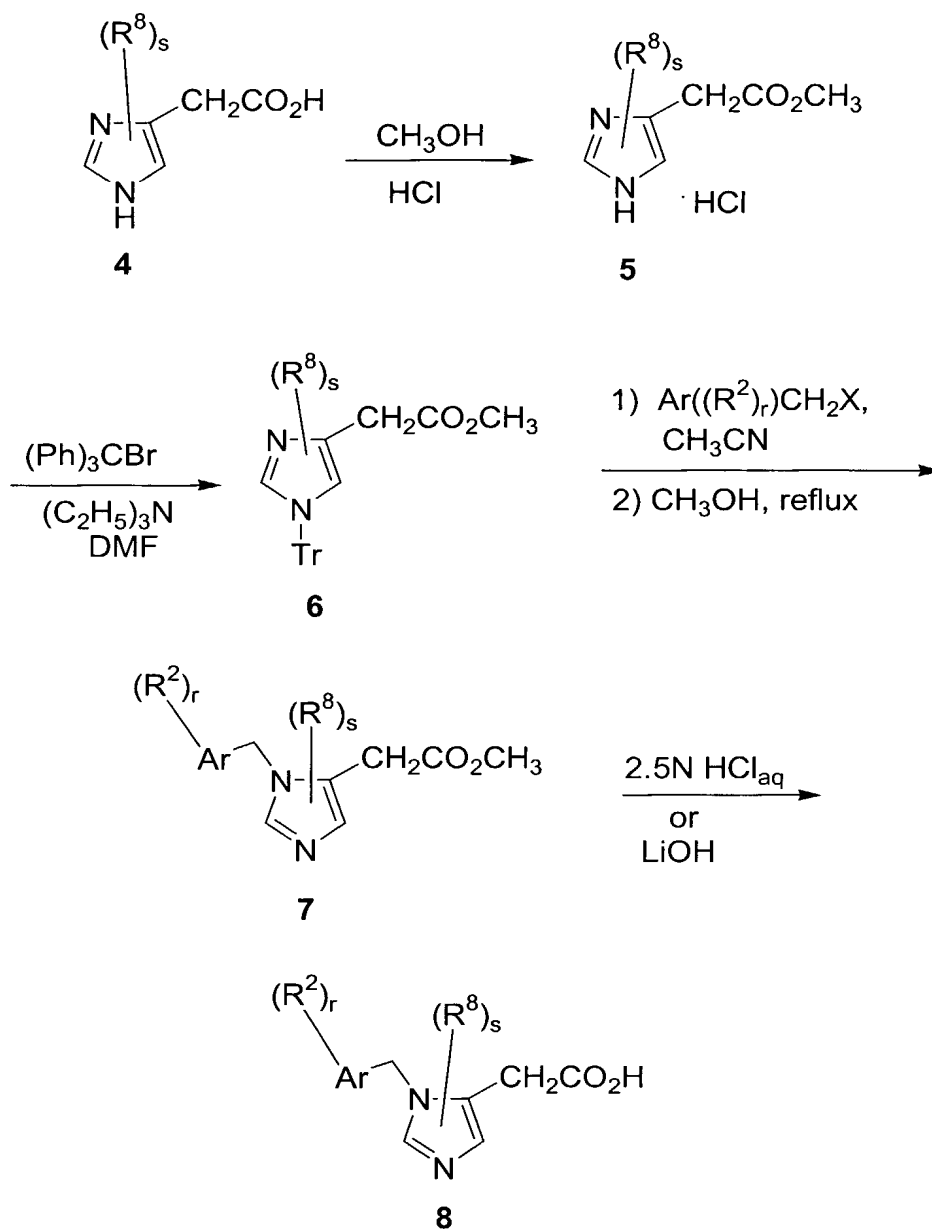
Schemes 19-22 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

SCHEME 1

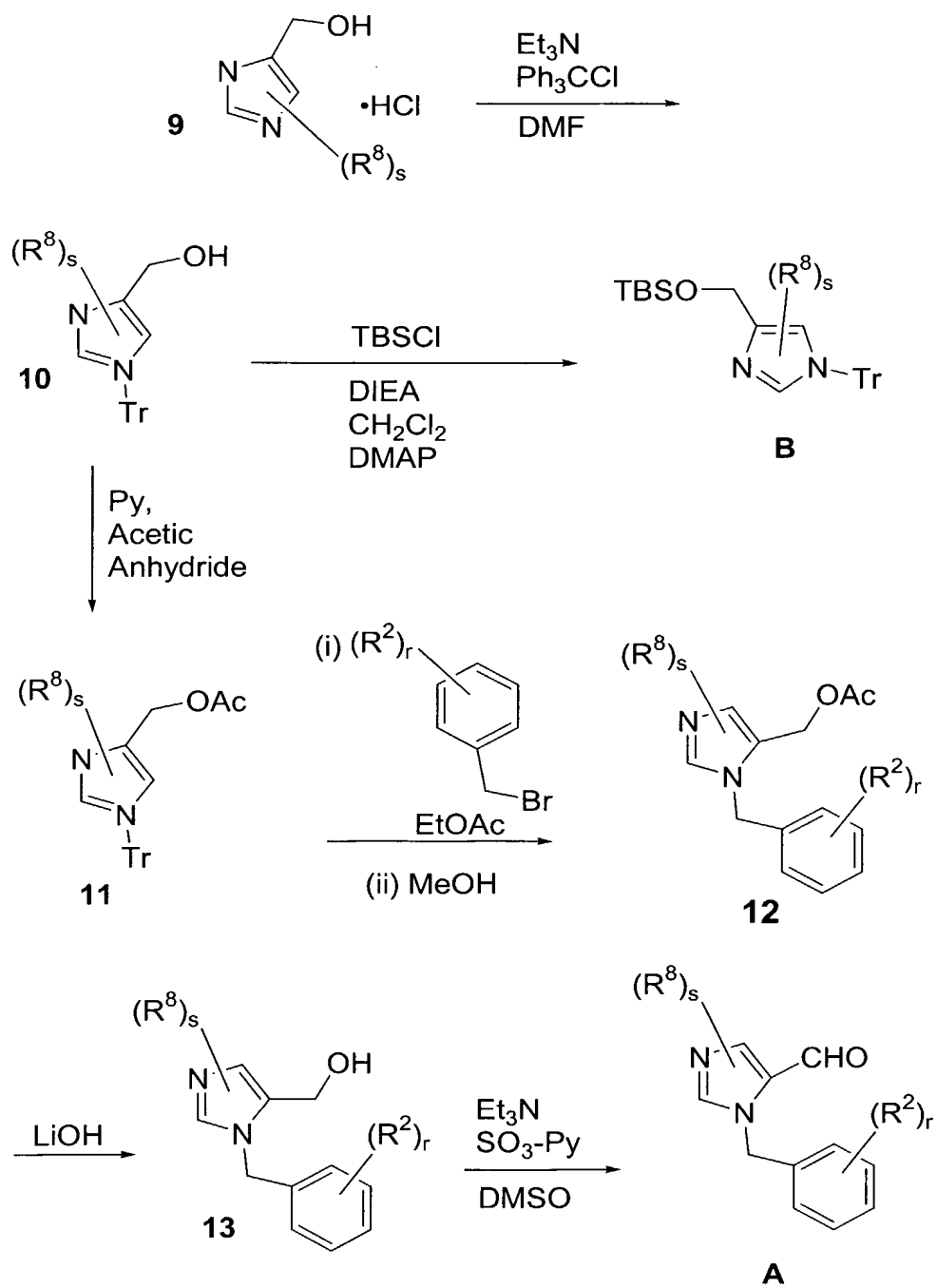
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SCHEME 2

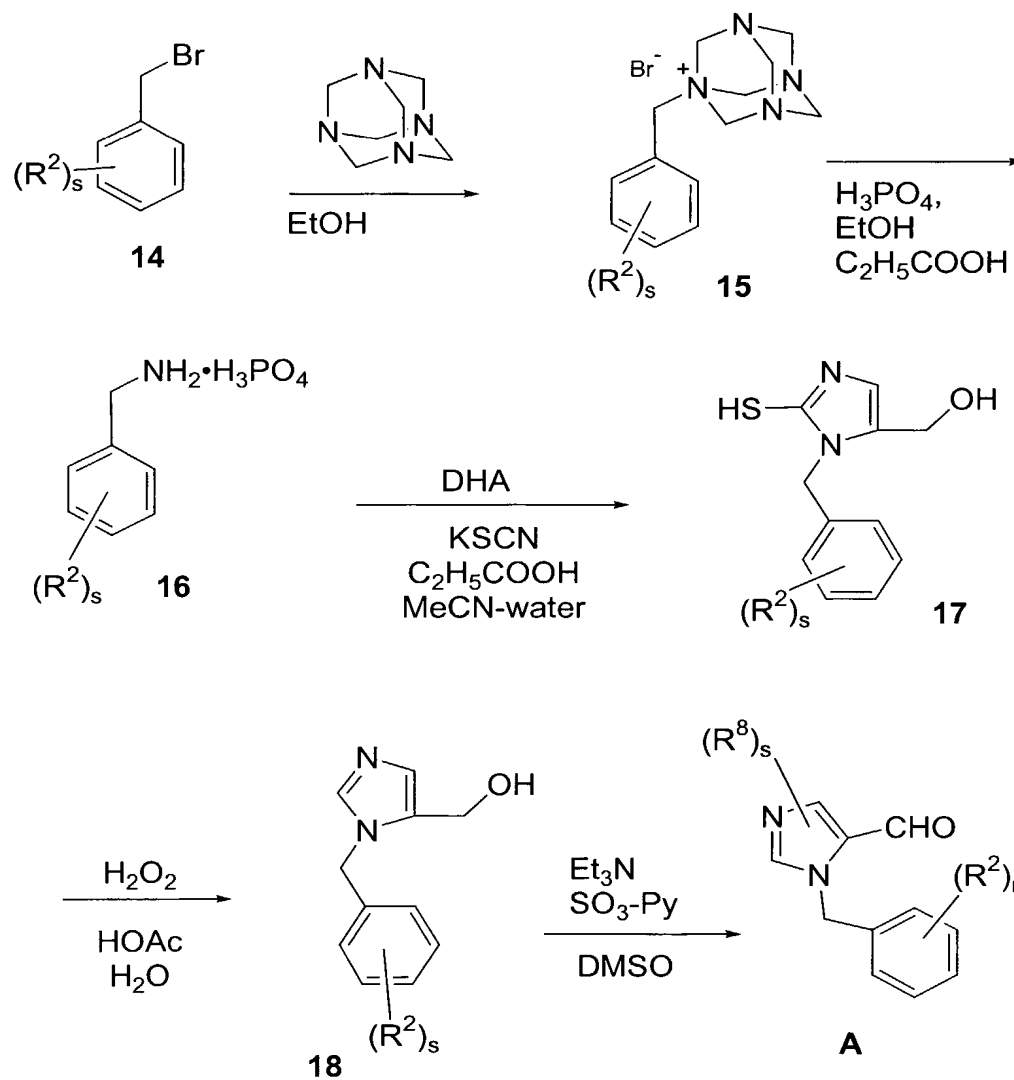
SCHEME 3



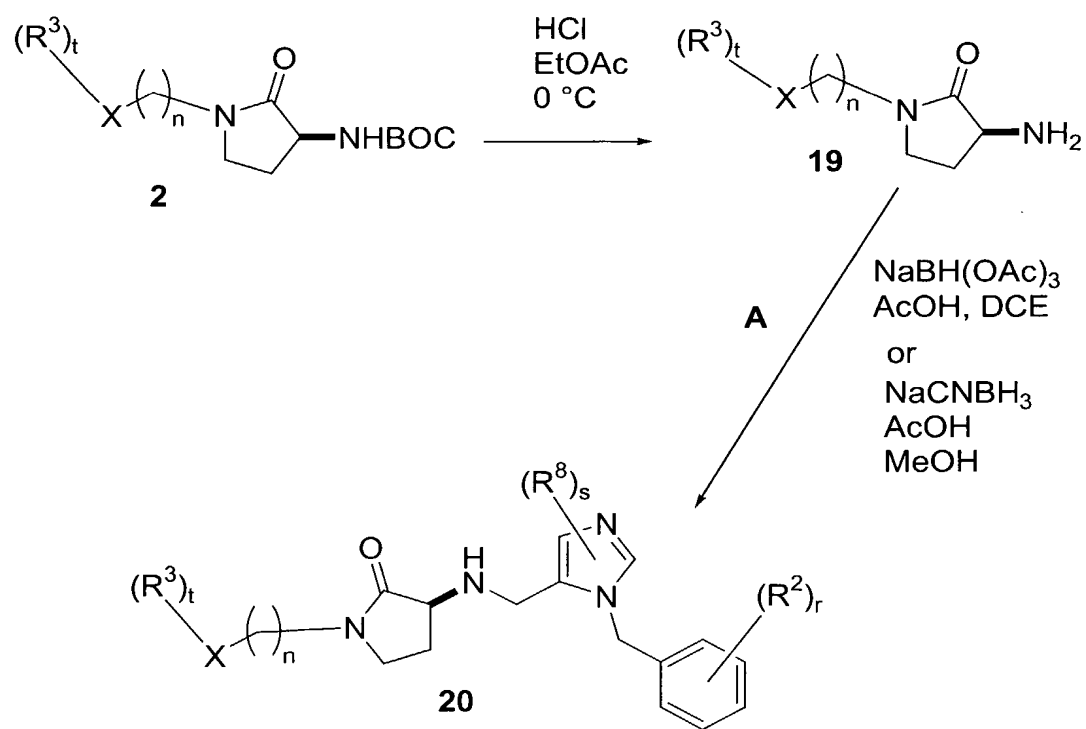
SCHEME 3A



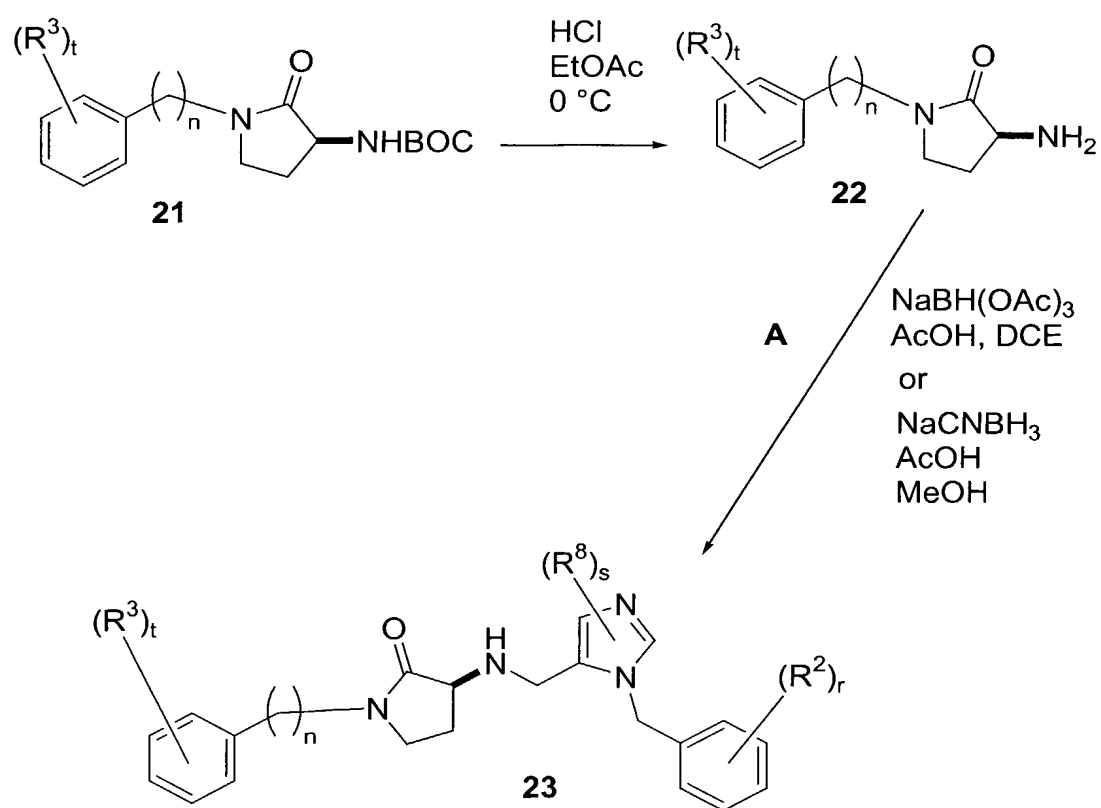
SCHEME 3B

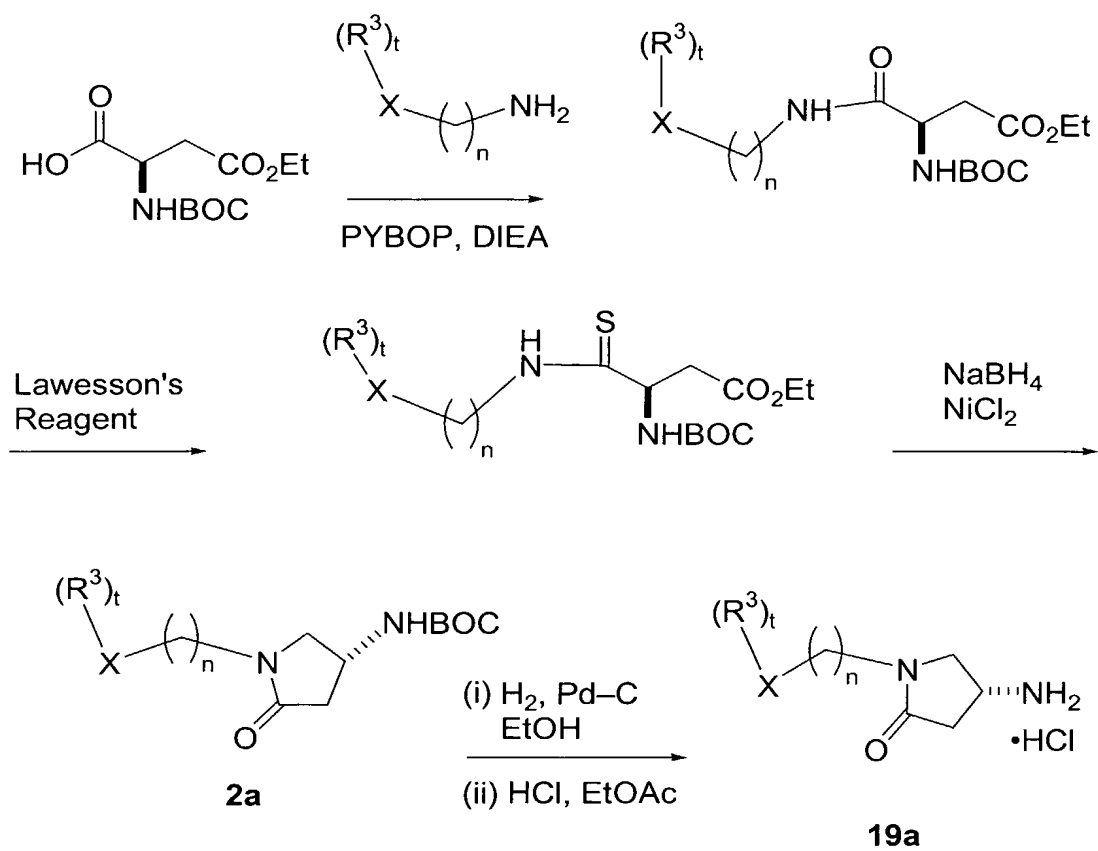


SCHEME 4

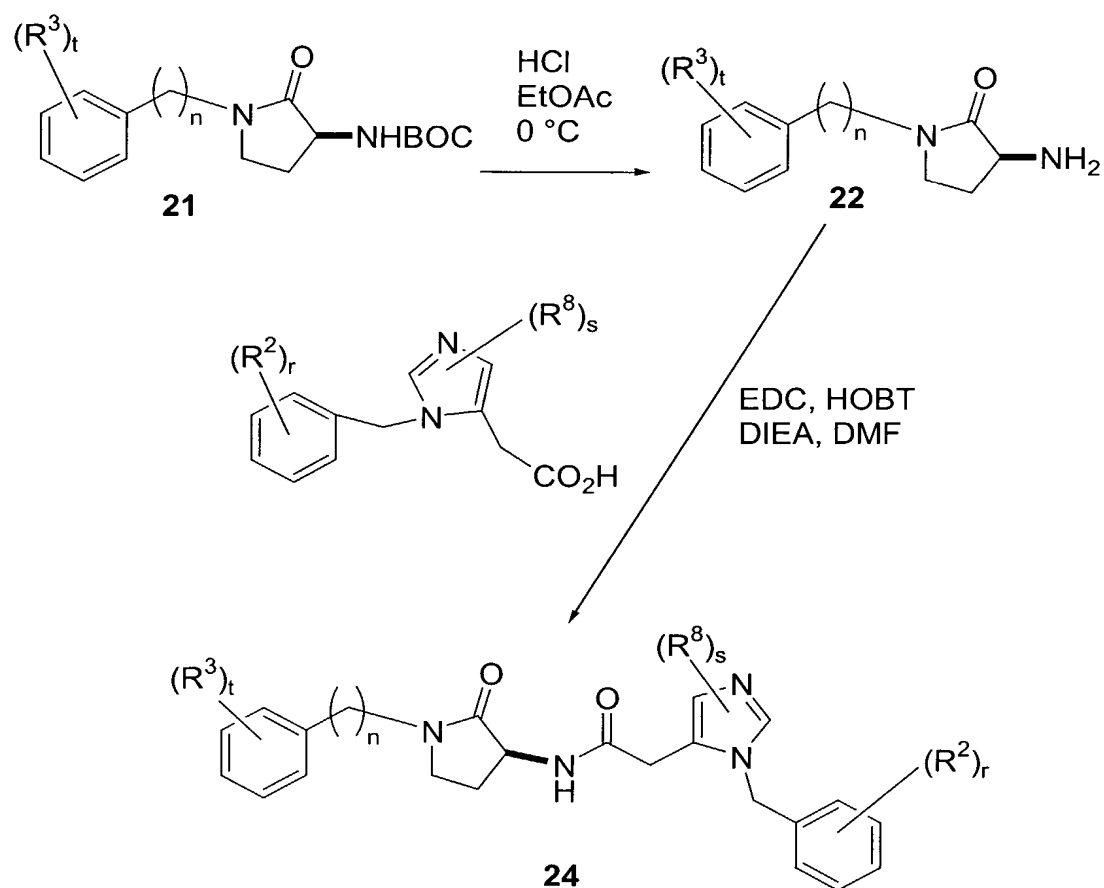


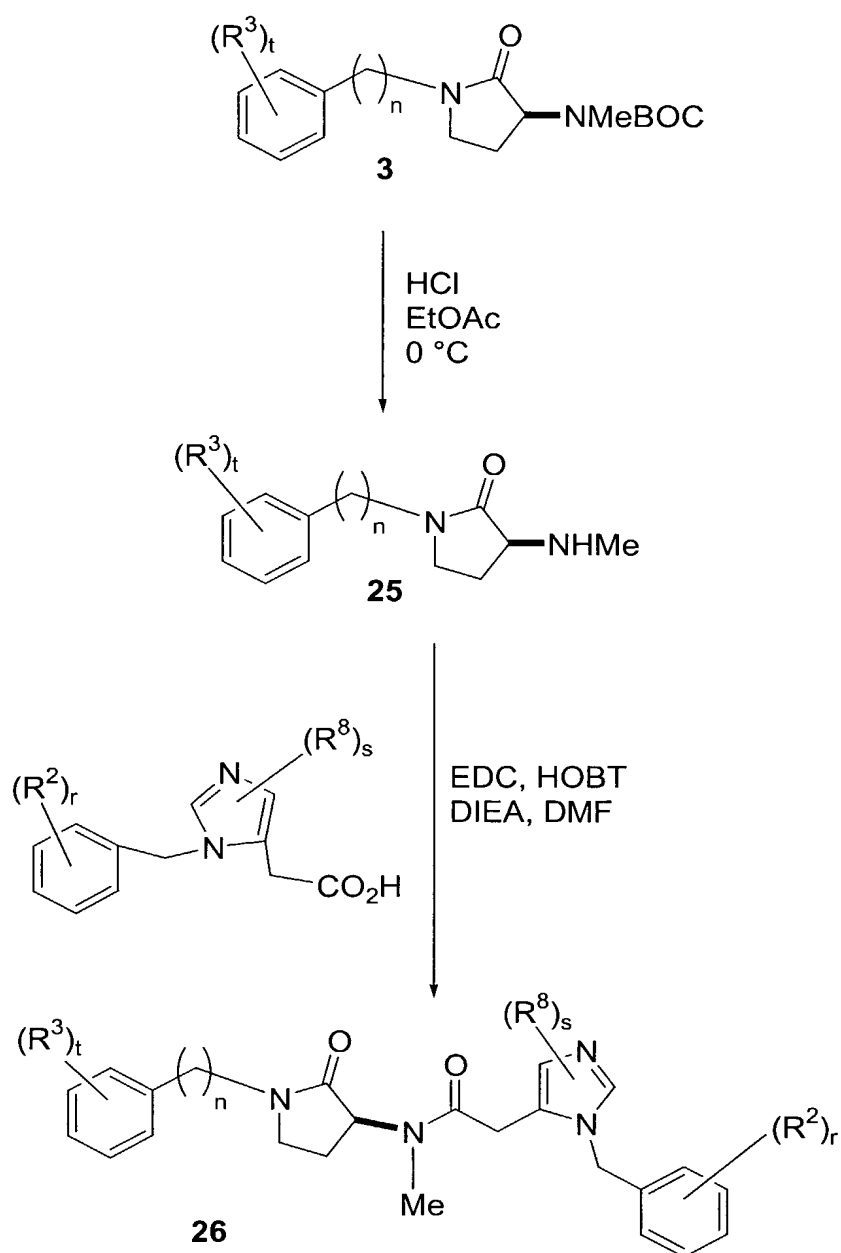
SCHEME 5

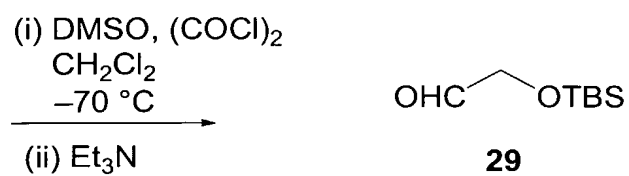
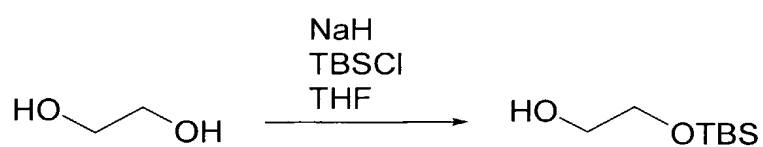
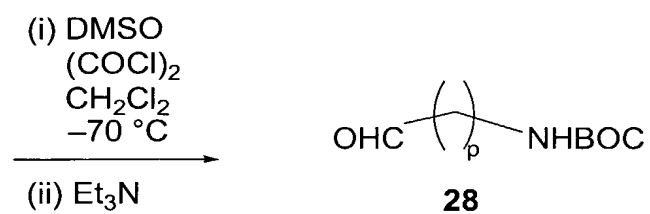
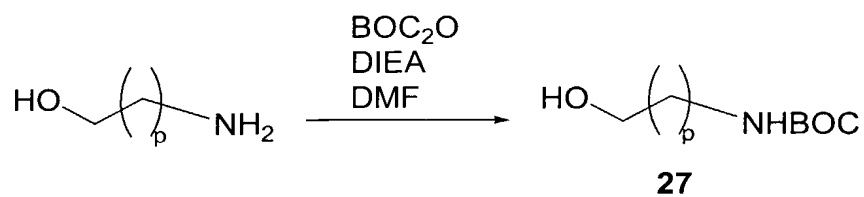




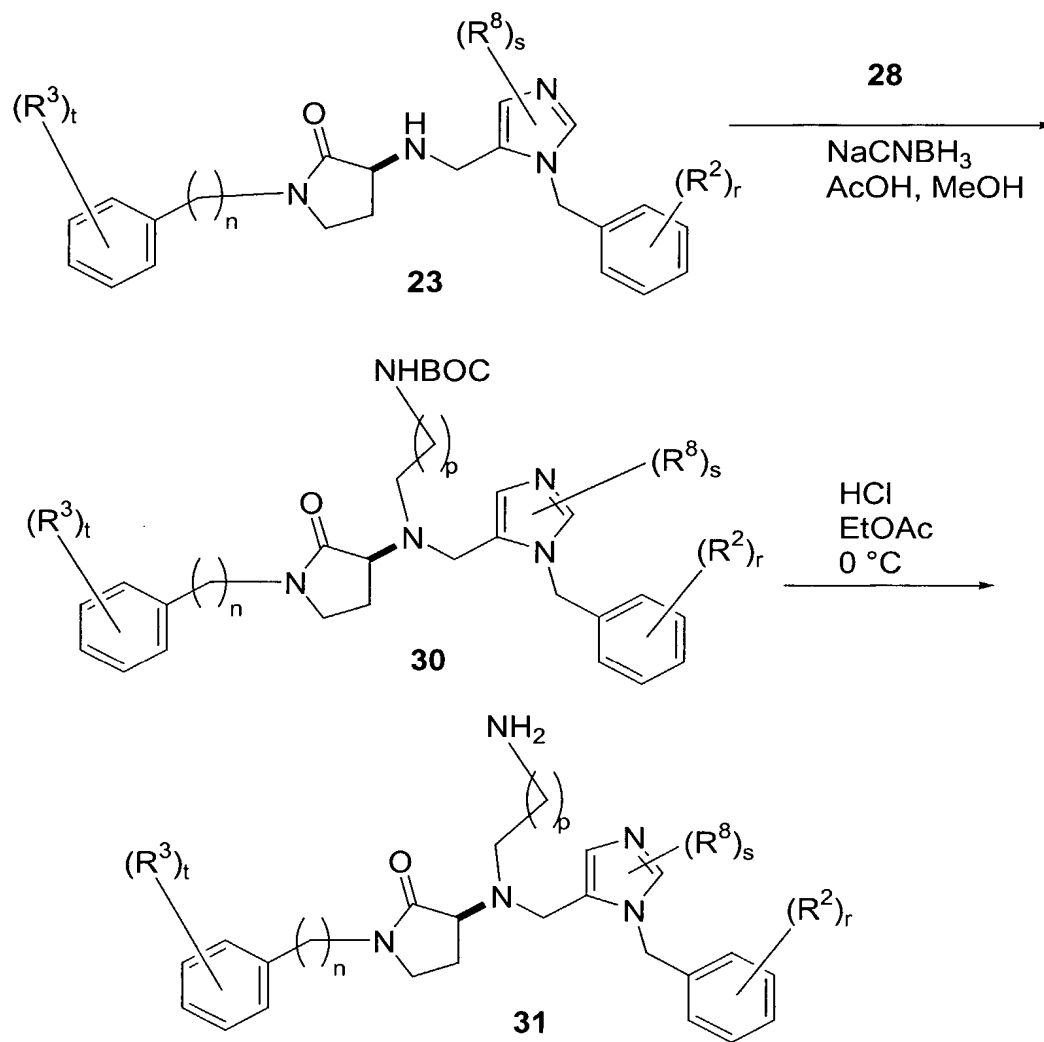
SCHEME 6



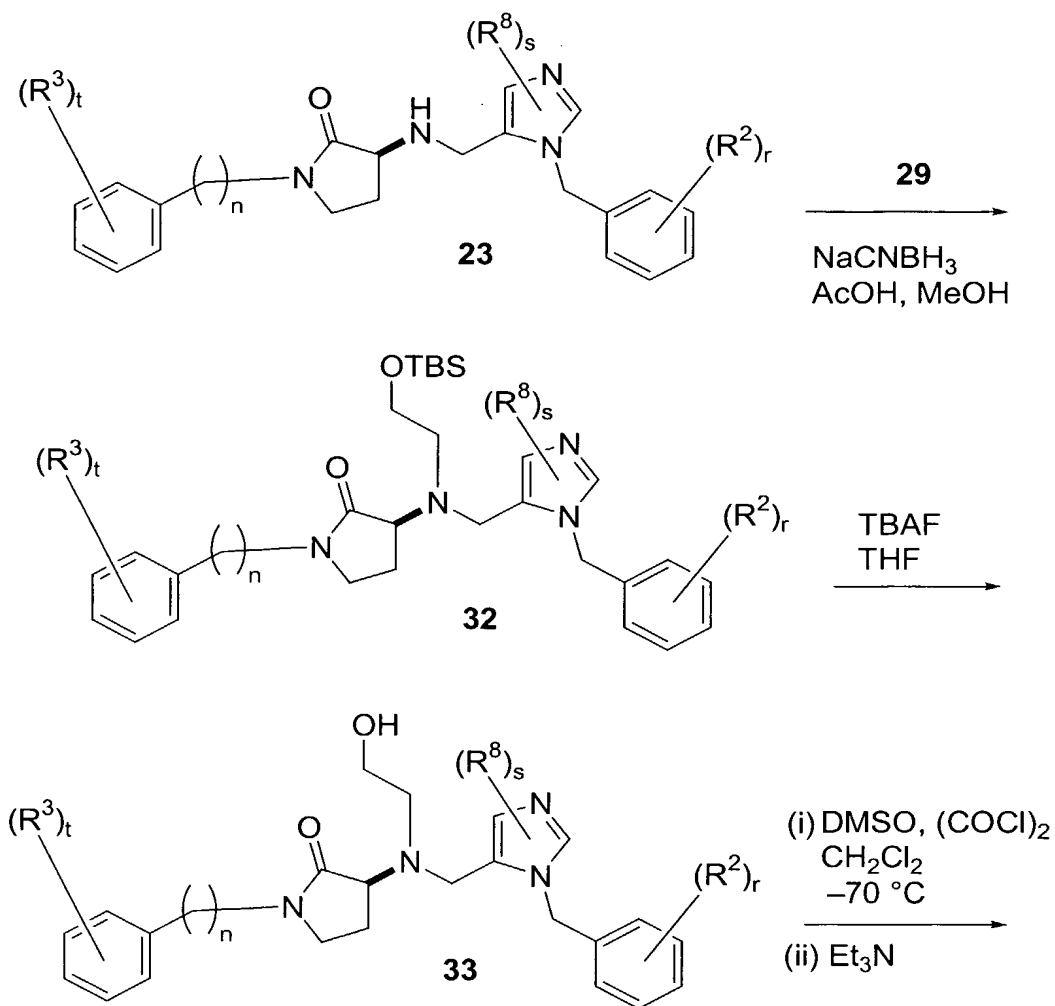
SCHEME 7

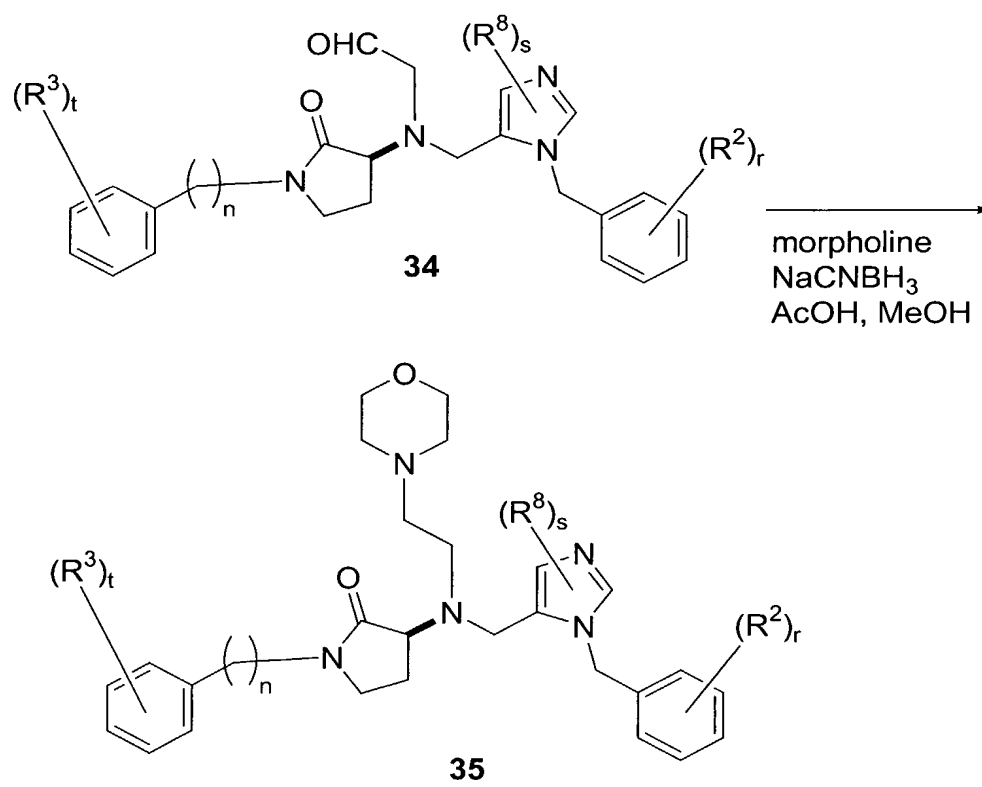
SCHEME 8

SCHEME 9

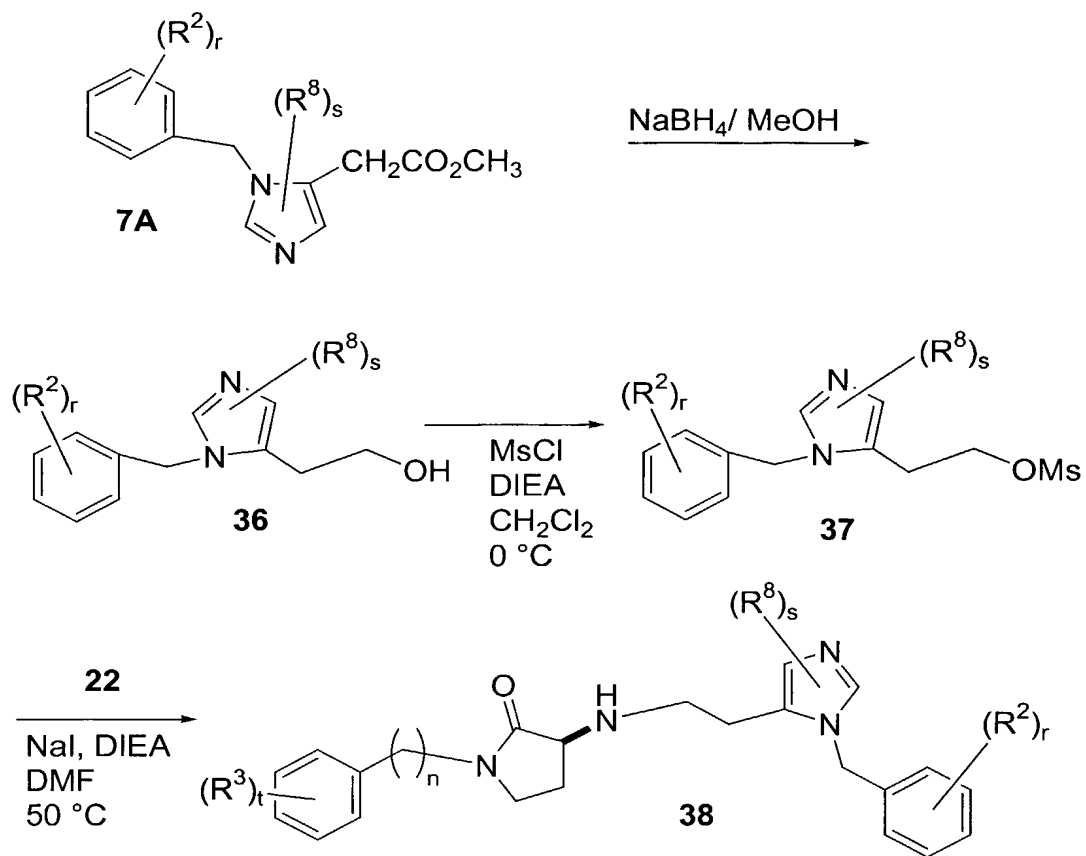


SCHEME 10

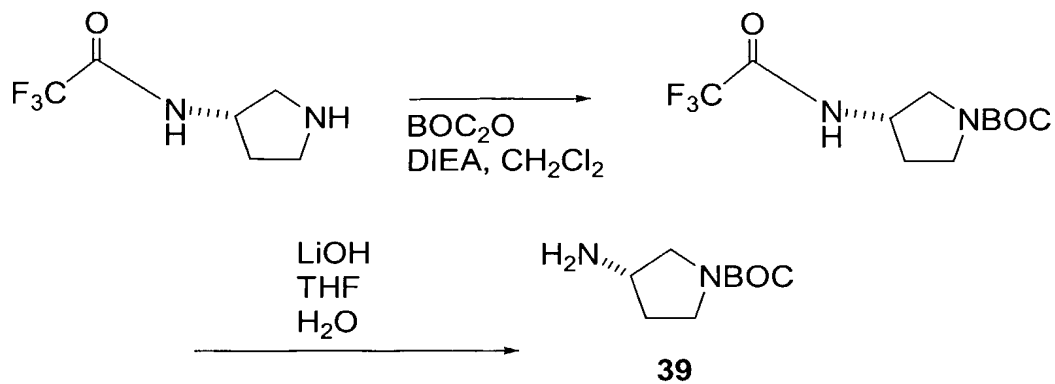


SCHEME 10 (CONTD)

SCHEME 11

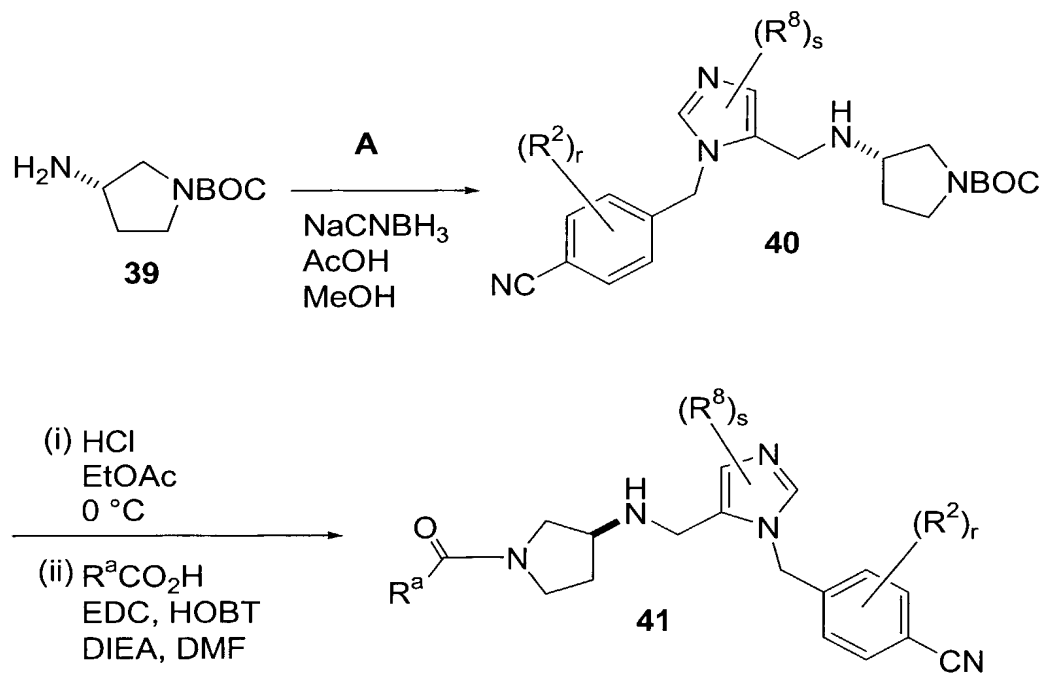


SCHEME 12

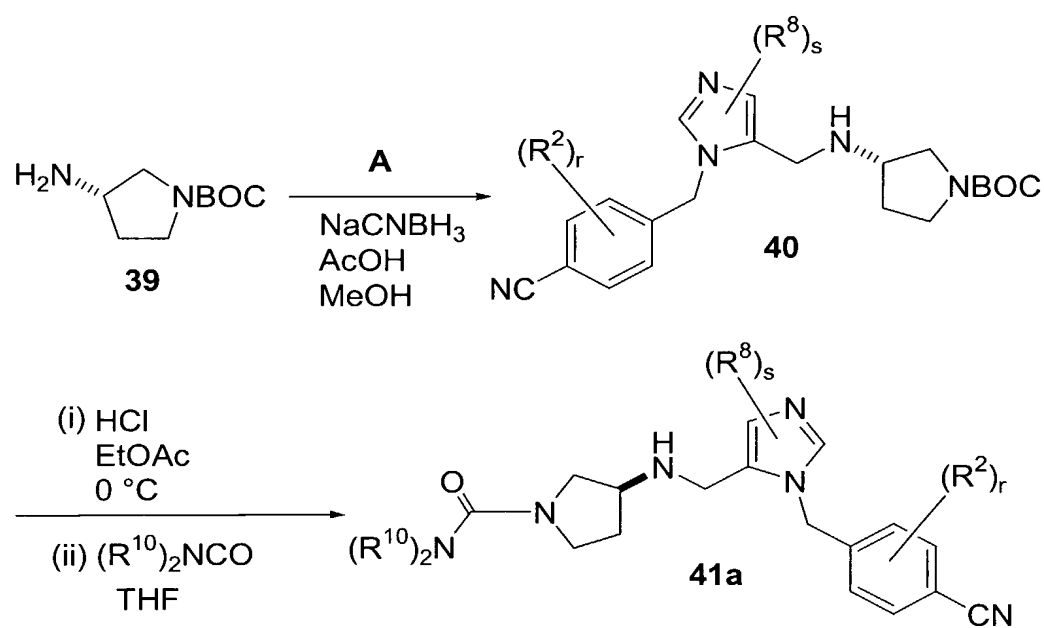


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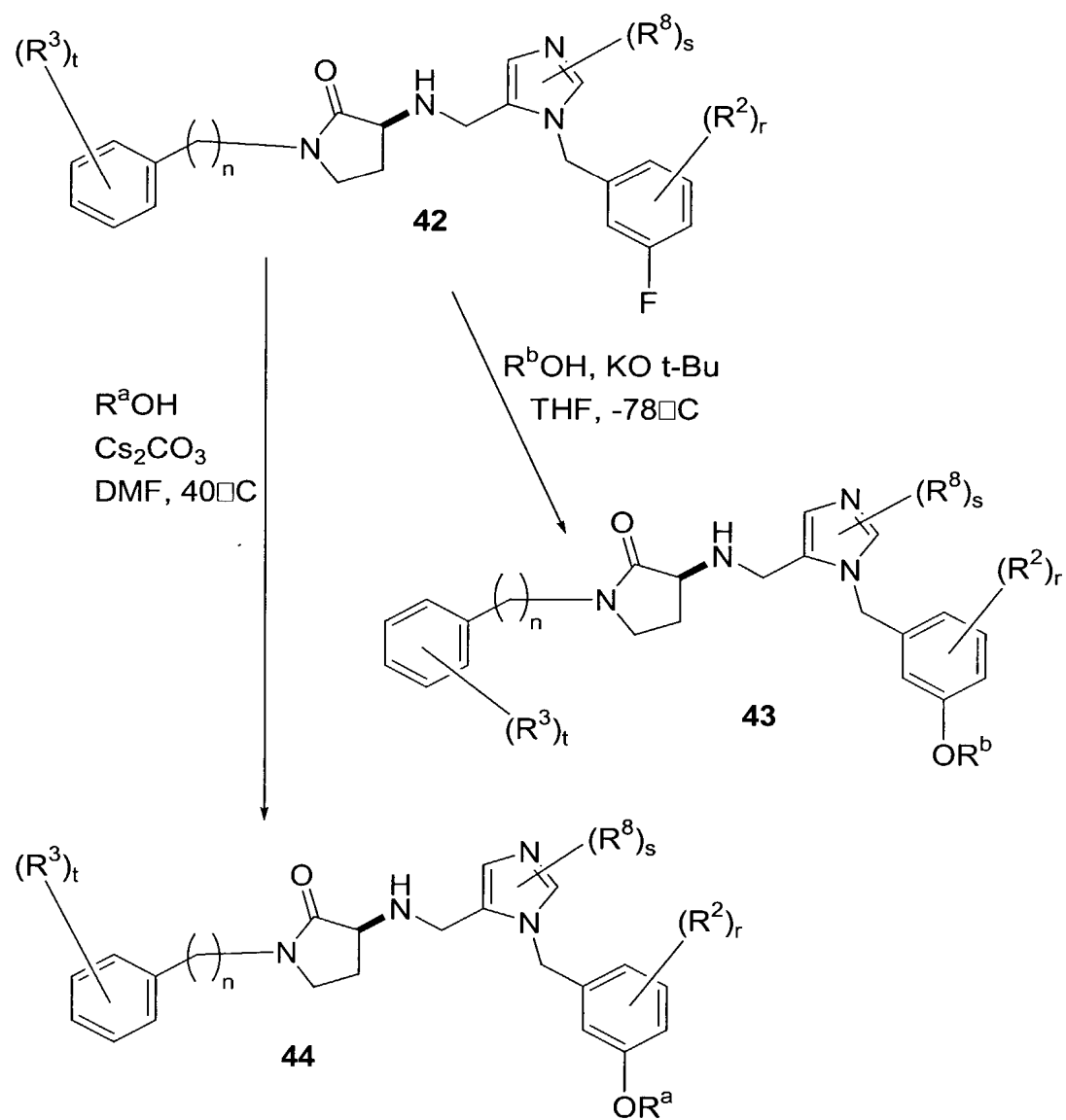
SCHEME 13



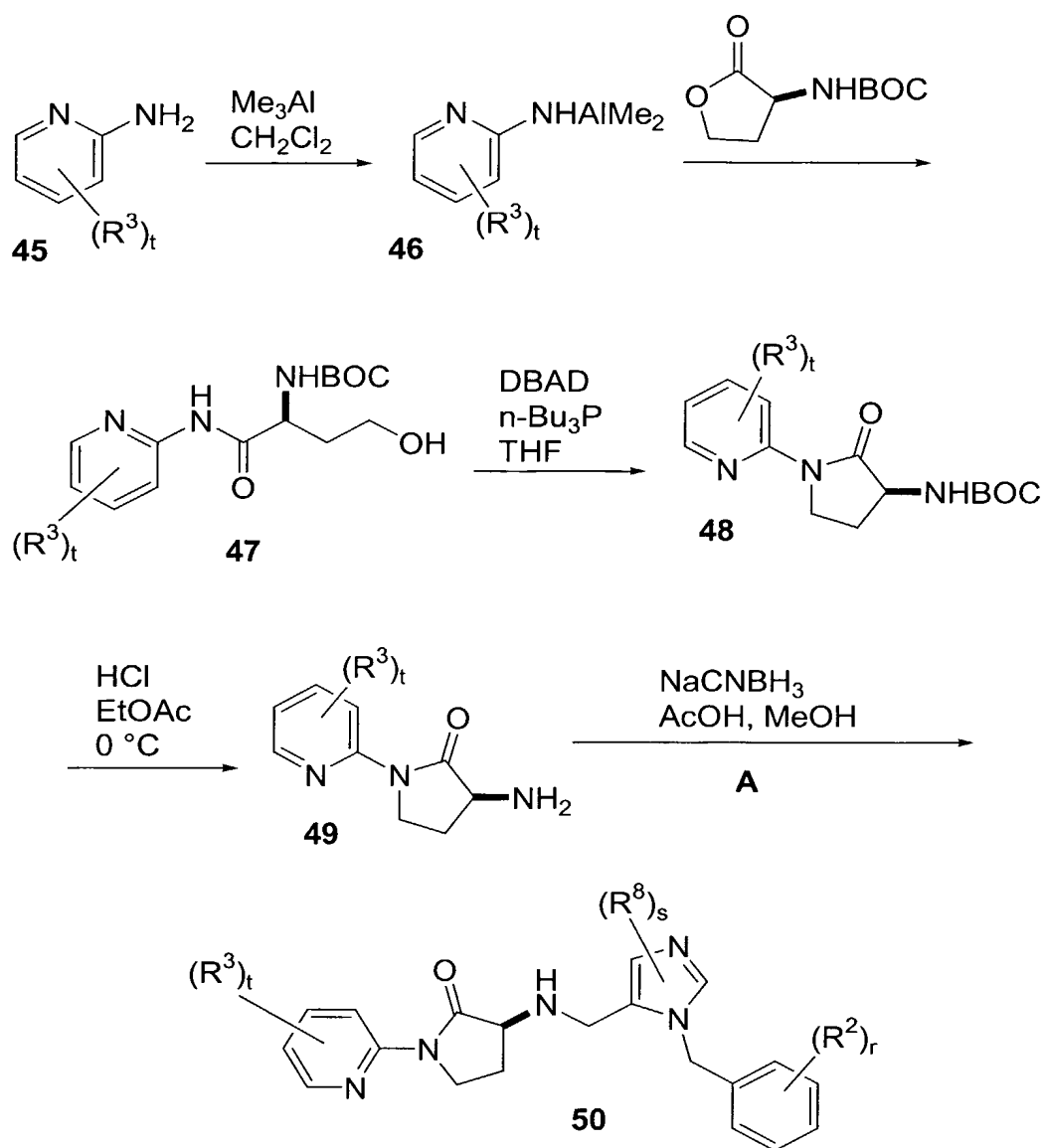
SCHEME 13A



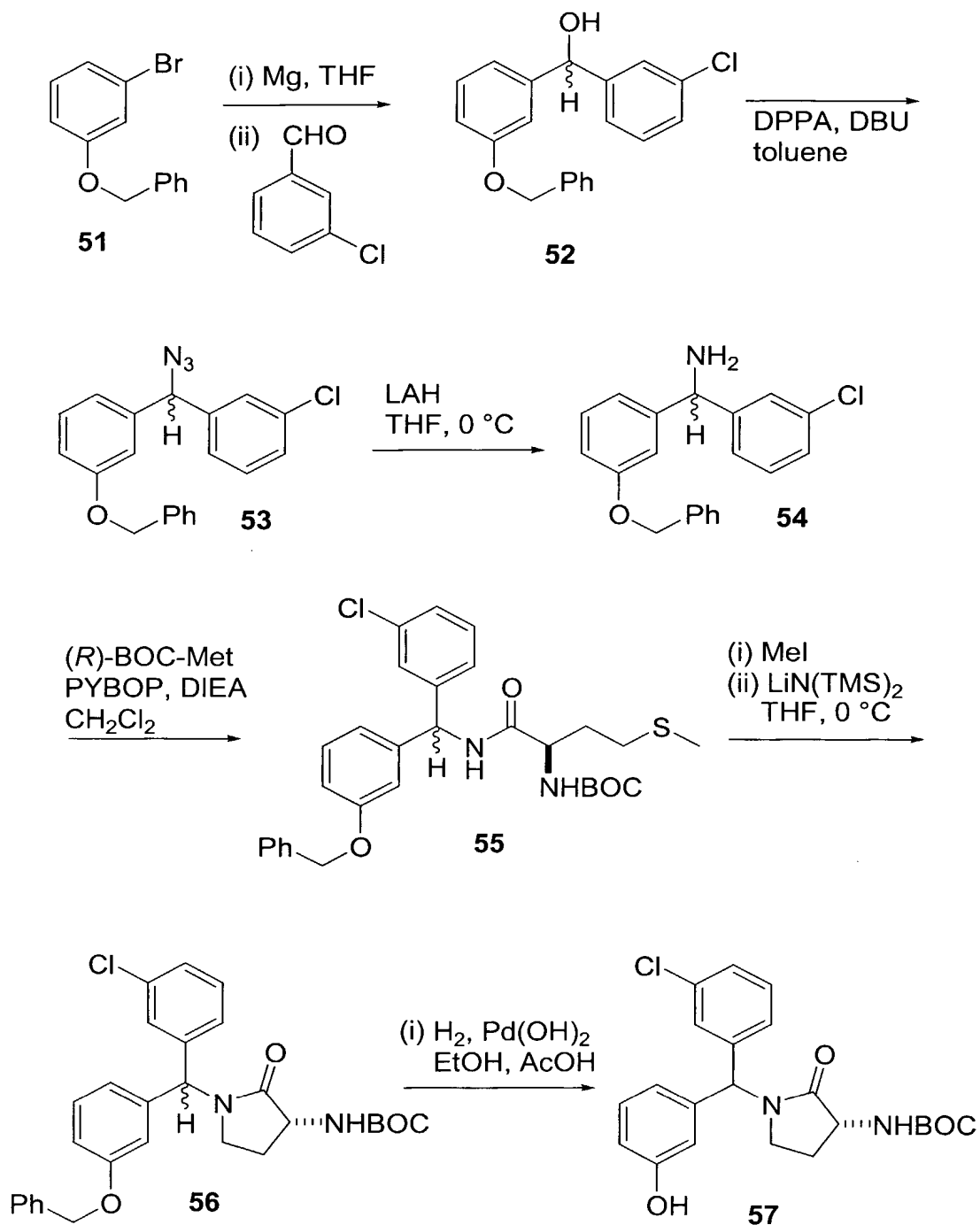
SCHEME 14



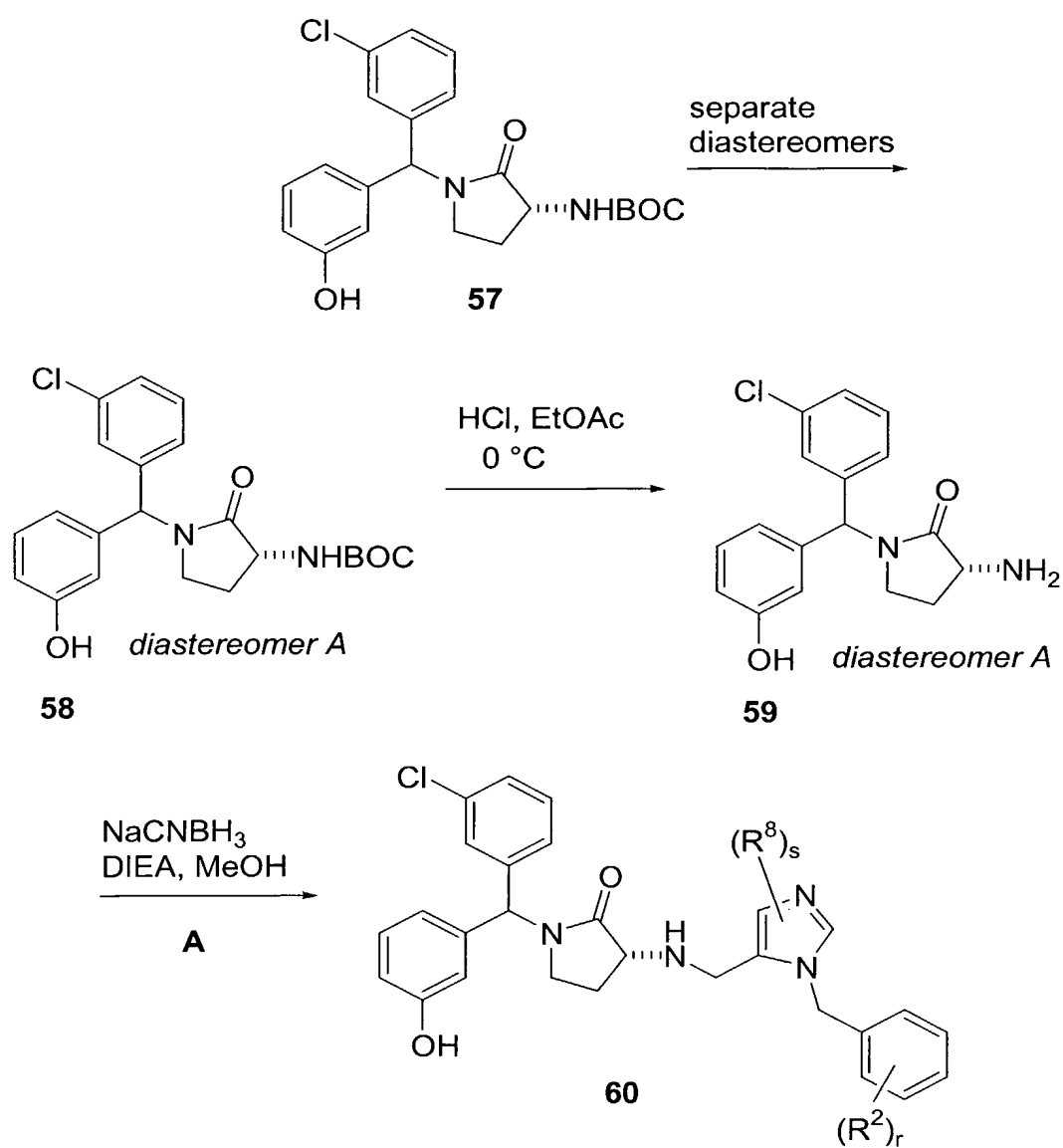
SCHEME 15



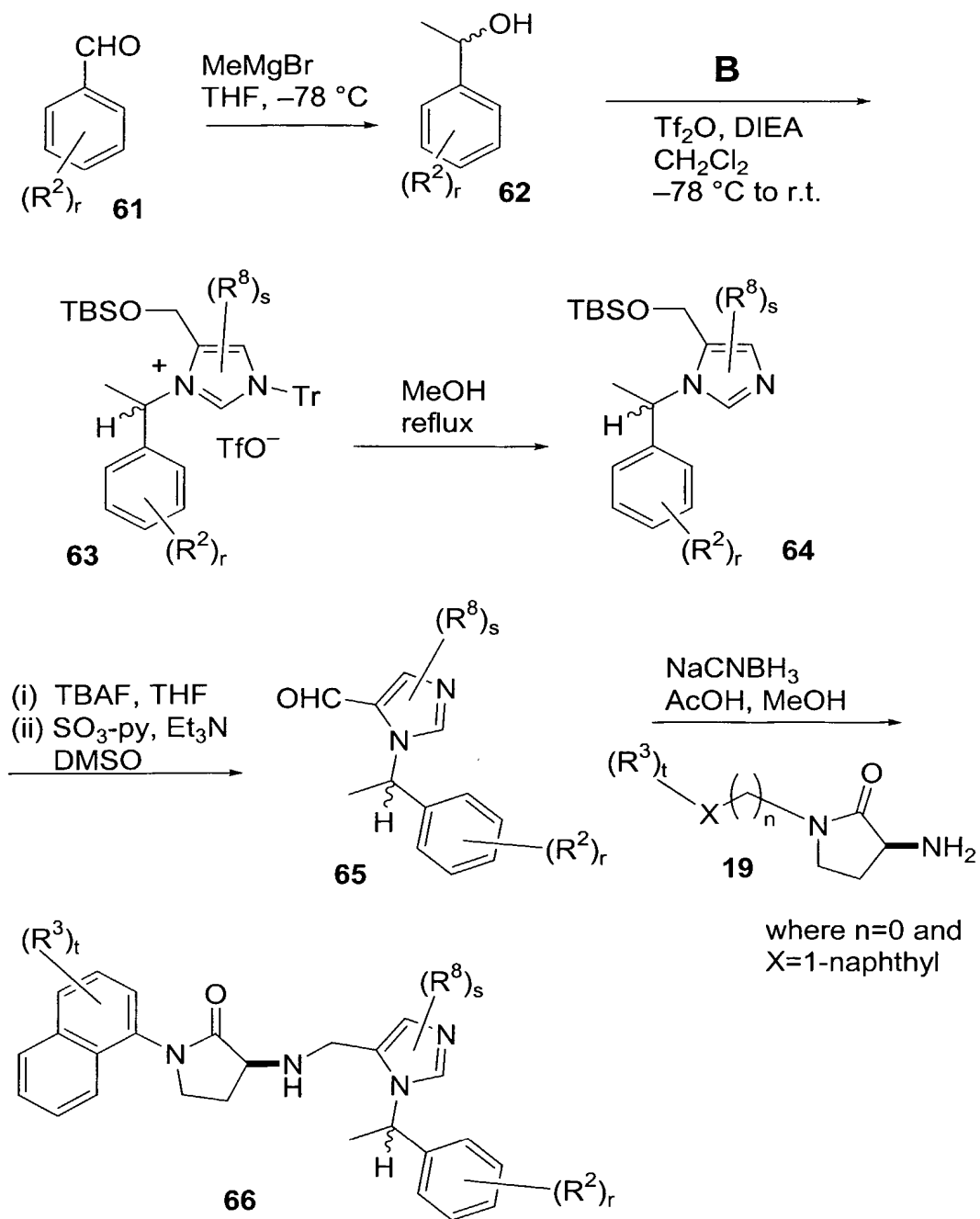
SCHEME 16



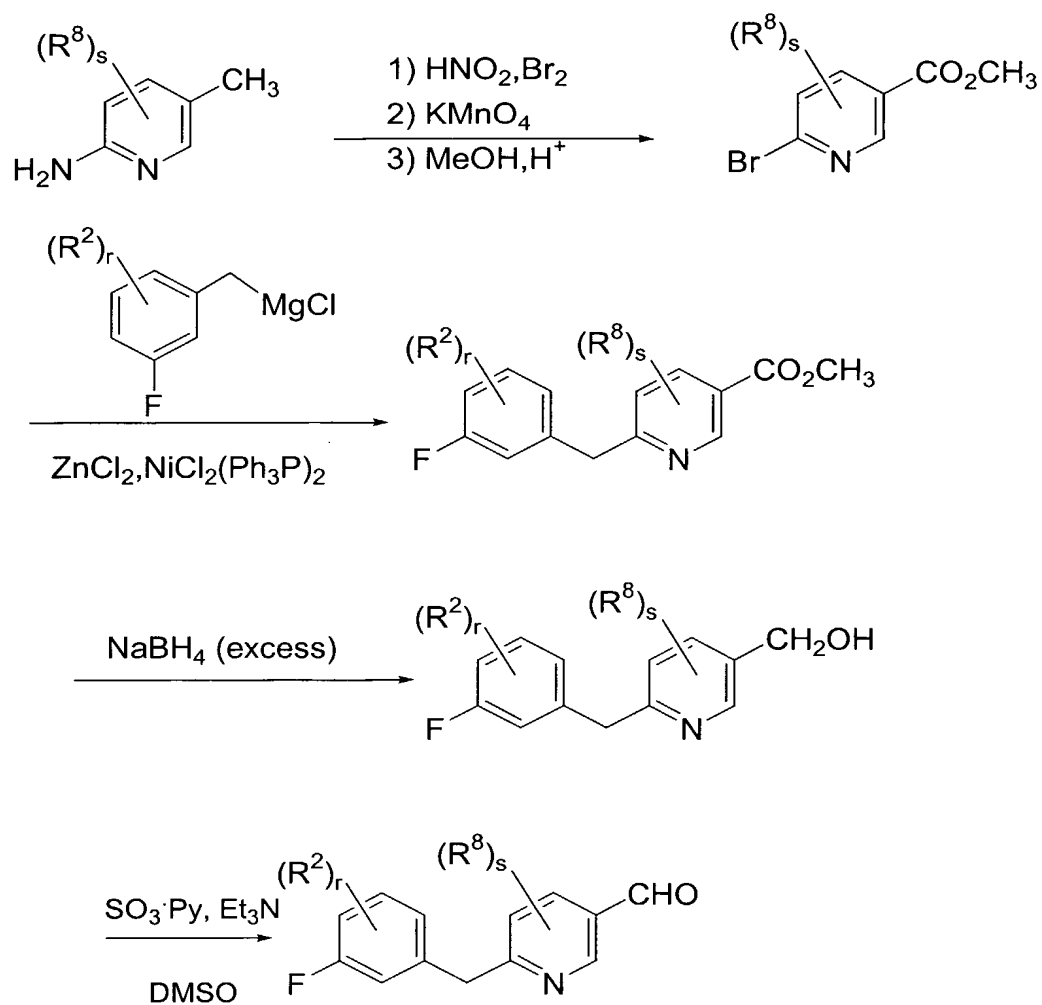
SCHEME 17



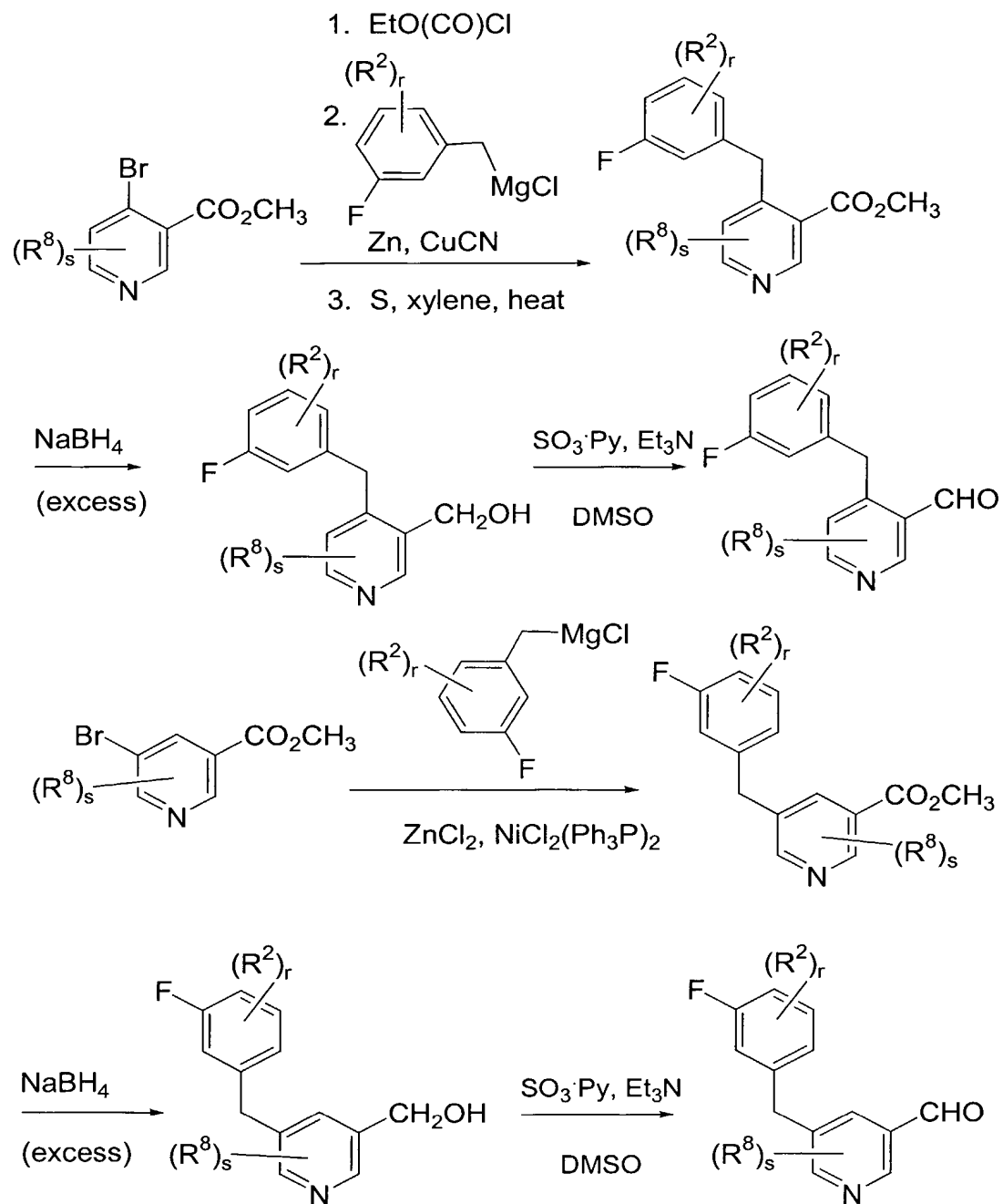
SCHEME 18



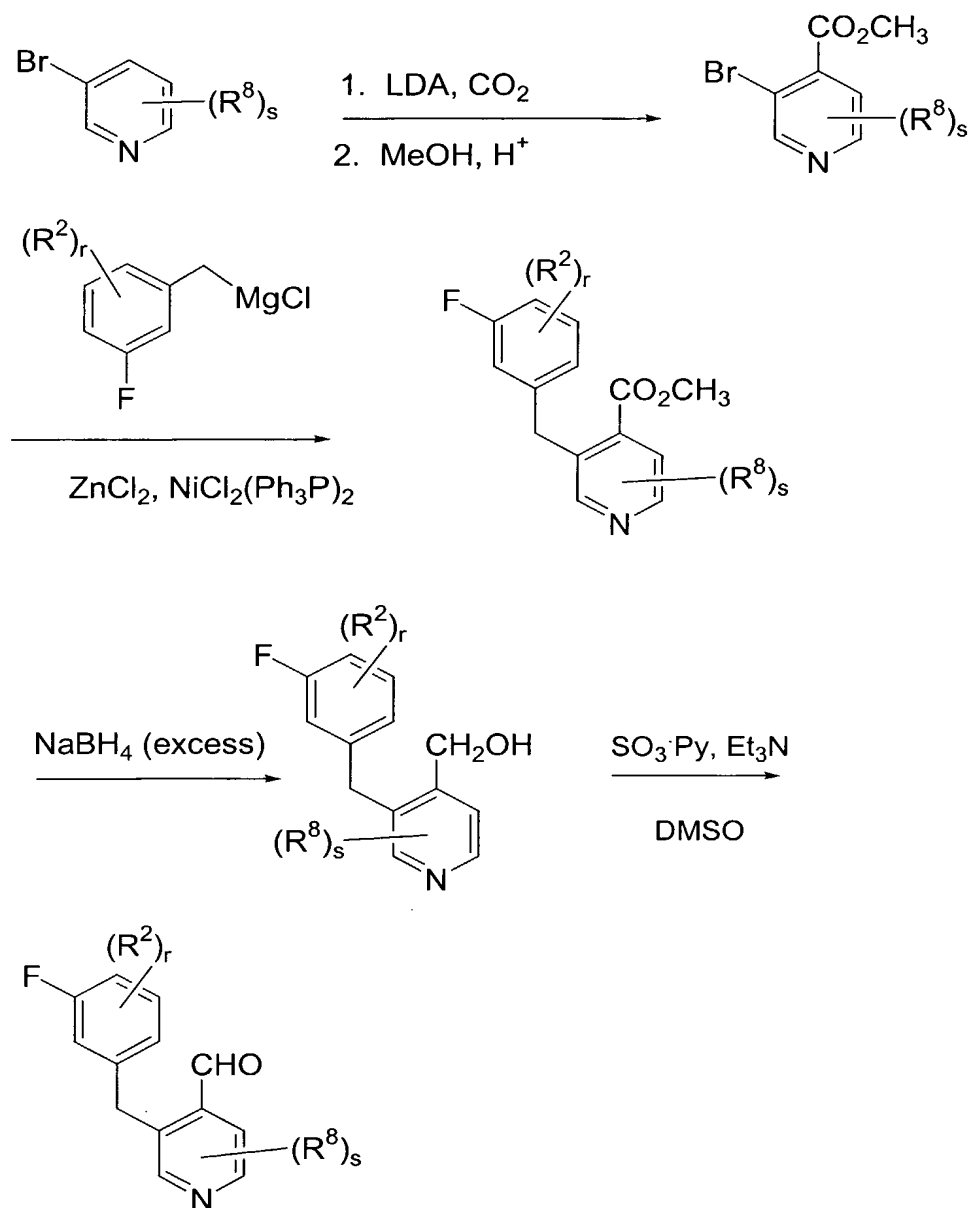
SCHEME 19



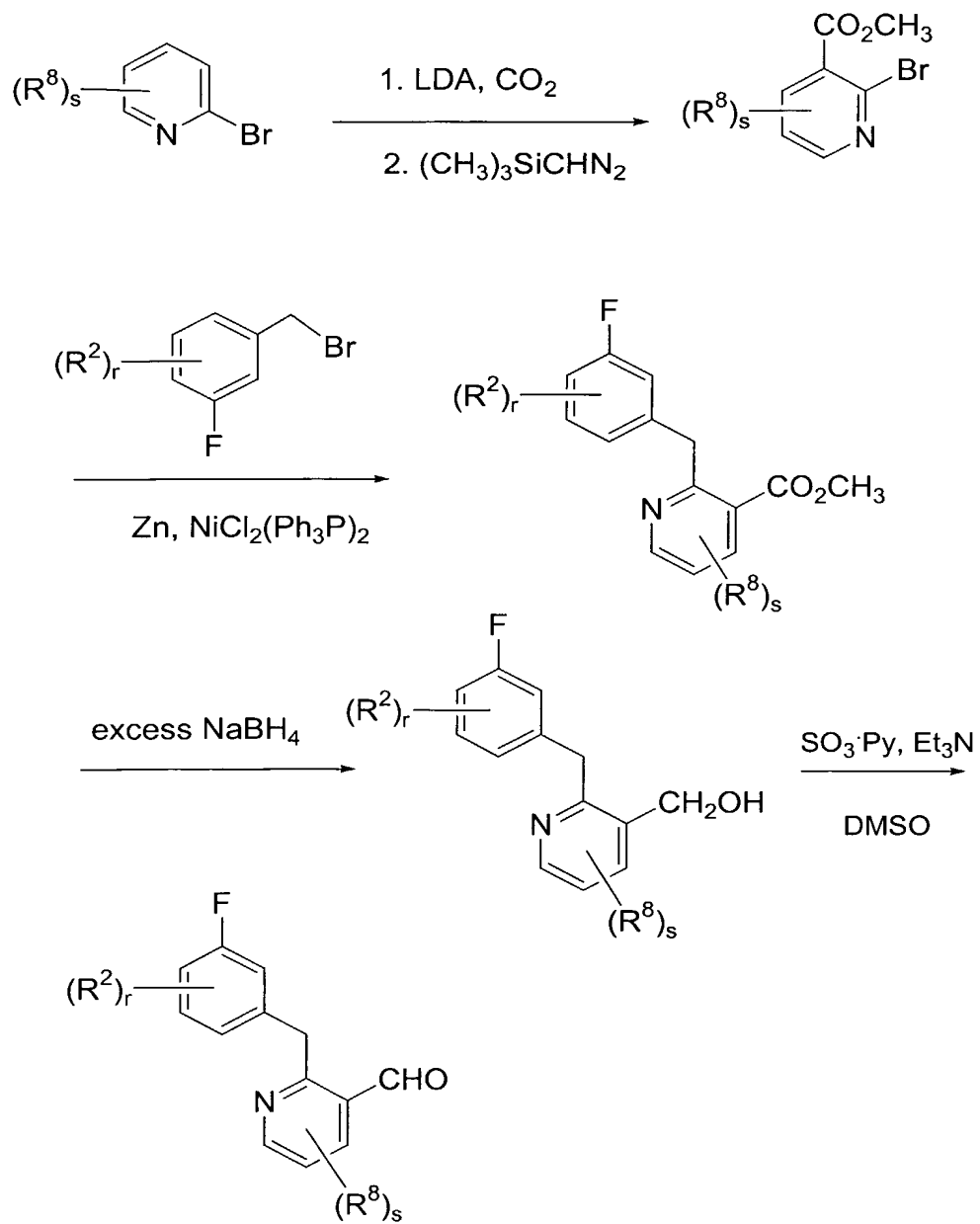
SCHEME 20


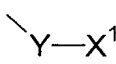


SCHEME 21



SCHEME 22



In the above Schemes, it is understood that  represents , unless otherwise indicated;

Ph represents phenyl;

Ar represents a carbocyclic or heterocyclic, substituted or
5 unsubstituted aromatic ring;

R^a represents an unsubstituted or substituted aryl or an unsubstituted or substituted heteroaryl; and

R^b represents an unsubstituted or substituted aralkyl or an
unsubstituted or substituted heterocyclalkyl.

10 In a preferred embodiment of the instant invention the compounds of the invention are selective inhibitors of farnesyl-protein transferase. A compound is considered a selective inhibitor of farnesyl-protein transferase, for example, when its *in vitro* farnesyl-protein transferase inhibitory activity, as assessed by the assay described in Example 177, is at least 100 times greater than the *in vitro* activity of
15 the same compound against geranylgeranyl-protein transferase-type I in the assay described in Example 178. Preferably, a selective compound exhibits at least 1000 times greater activity against one of the enzymatic activities when comparing geranylgeranyl-protein transferase-type I inhibition and farnesyl-protein transferase inhibition.

20 It is also preferred that the selective inhibitor of farnesyl-protein transferase is further characterized by:

a) an IC₅₀ (a measure of *in vitro* inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than about 100-fold higher than the EC₅₀ for the inhibition of the farnesylation of hDJ protein. When
25 measuring such IC₅₀s and EC₅₀s the assays described in Example 182 may be utilized.

It is also preferred that the selective inhibitor of farnesyl-protein transferase is further characterized by:

b) an IC₅₀ (a measurement of *in vitro* inhibitory activity) for inhibition of K4B-Ras dependent activation of MAP kinases in cells at least 100-fold
30 greater than the EC₅₀ for inhibition of the farnesylation of the protein hDJ in cells.

It is also preferred that the selective inhibitor of farnesyl-protein transferase is further characterized by:

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells at least 1000 fold lower than the inhibitory activity (IC_{50}) against H-ras-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells. When measuring Ras dependent activation of MAP kinases in cells the assays described in Example 181 may be utilized.

In another preferred embodiment of the instant invention the compounds of the invention are dual inhibitors of farnesyl-protein transferase and geranylgeranyl-protein transferase type I. Such a dual inhibitor may be termed a Class II prenyl-protein transferase inhibitor and will exhibit certain characteristics when assessed in *in vitro* assays, which are dependent on the type of assay employed.

In a SEAP assay, such as described in Example 181, it is preferred that the dual inhibitor compound has an *in vitro* inhibitory activity (IC_{50}) that is less than about 12 μ M against K4B-Ras dependent activation of MAP kinases in cells.

The Class II prenyl-protein transferase inhibitor may also be characterized by:

- a) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibiting K4B-Ras dependent activation of MAP kinases in cells between 0.1 and 100 times the IC_{50} for inhibiting the farnesylation of the protein hDJ in cells; and
- b) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibiting K4B-Ras dependent activation of MAP kinases in cells greater than 5-fold lower than the inhibitory activity (IC_{50}) against expression of the SEAP protein in cells transfected with the pCMV-SEAP plasmid that constitutively expresses the SEAP protein.

The Class II prenyl-protein transferase inhibitor may also be characterized by:

- a) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells greater than 2 fold lower but less than 20,000 fold lower than the inhibitory activity (IC_{50}) against H-ras-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells; and
- b) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-ras-CVLL dependent activation of MAP kinases in cells greater than 5-fold lower than the inhibitory activity (IC_{50}) against expression of the SEAP protein in cells transfected with the pCMV-SEAP plasmid that constitutively expresses the SEAP protein.

The Class II prenyl-protein transferase inhibitor may also be characterized by:

- a) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells greater than 10-fold lower but less than 2,500 fold lower than the inhibitory activity (IC_{50}) against H-ras-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells; and
- b) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-ras-CVLL dependent activation of MAP kinases in cells greater than 5 fold lower than the inhibitory activity (IC_{50}) against expression of the SEAP protein in cells transfected with the pCMV-SEAP plasmid that constitutively expresses the SEAP protein.

A method for measuring the activity of the inhibitors of prenyl-protein transferase, as well as the instant combination compositions, utilized in the instant methods against Ras dependent activation of MAP kinases in cells is described in Example 181.

In yet another embodiment, a compound of the instant invention may be a more potent inhibitor of geranylgeranyl-protein transferase-type I than it is an inhibitor of farnesyl-protein transferase.

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, src, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of vision deficit related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras

gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, the composition is useful in the treatment of neurofibromatosis, which is a benign proliferative disorder.

5 The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

 The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by
10 inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

 The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

15 The instant compounds may also be useful for the treatment of fungal infections.

 The instant compounds may also be useful as inhibitors of proliferation of vascular smooth muscle cells and therefore useful in the prevention and therapy of arteriosclerosis and diabetic vascular pathologies.

20 The compounds of the instant invention may also be useful in the prevention and treatment of endometriosis, uterine fibroids, dysfunctional uterine bleeding and endometrial hyperplasia.

 In such methods of prevention and treatment as described herein, the prenyl-protein transferase inhibitors of the instant invention may also be co-
25 administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the prenyl-protein transferase inhibitor may be useful in further combination with drugs known to suppress the activity of the ovaries and slow the growth of the endometrial tissue. Such drugs include but are not limited to oral contraceptives, progestins,
30 danazol and GnRH (gonadotropin-releasing hormone) agonists.

 Administration of the prenyl-protein transferase inhibitor may also be combined with surgical treatment of endometriosis (such as surgical removal of misplaced endometrial tissue) where appropriate.

35 The instant compounds may also be useful as inhibitors of corneal inflammation. These compounds may improve the treatment of corneal opacity which

results from cauterization-induced corneal inflammation. The instant compounds may also be useful in reducing corneal edema and neovascularization. (K. Sonoda et al., *Invest. Ophthalmol. Vis. Sci.*, 1998, vol. 39, p 2245-2251).

5 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

10 Additionally, the compounds of the instant invention may be administered to a mammal in need thereof using a gel extrusion mechanism (GEM) device, such as that described in USSN 60/144,643, filed on July 20, 1999, which is hereby incorporated by reference.

15 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous
20 or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order
25 to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for
30 example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and

thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethylene glycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

10 Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring
15 phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
20 condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

25 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a
30 palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisole or alpha-tocopherol.

 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more
35 preservatives. Suitable dispersing or wetting agents and suspending agents are

exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 The pharmaceutical compositions of the invention may also be
in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and
10 condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also
15 contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-
20 water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a
25 patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous
30 pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been

mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose
5 any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula A may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at
10 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions,
15 etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known
20 to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of
25 various molecular weights and fatty acid esters of polyethylene glycol.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

30 In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the compounds of the instant invention may also be co-administered with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic agents are combinations of the instant farnesyl-protein transferase inhibitors and an antineoplastic agent. It is also understood that such a combination of antineoplastic agent and inhibitor of farnesyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery. It is further understood that any of the therapeutic agents described herein may also be used in combination with a compound of the instant invention and an antineoplastic agent.

Examples of an antineoplastic agent include, in general, microtubule-stabilizing agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), epothilone A, epothilone B, desoxyepothilone A, desoxyepothilone B or their derivatives); microtubule-disruptor agents; alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulfonates and other compounds with an alkylating action such as nitrosoureas, cisplatin, and dacarbazine; anti-metabolites, for example, folic acid, purine or pyrimidine antagonists; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; cytotoxic antibiotics; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors and antibodies (such as trastuzumab (Herceptin™)).

Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estra-

mustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, tamoxifen, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU),
5 procarbazine, mitomycin, cytarabine, etoposide, methotrexate, bleomycin, chlorambucil, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins. Particular examples of antineoplastic, or chemotherapeutic, agents are described, for example, by D. J. Stewart in "Nausea and Vomiting: Recent Research and Clinical Advances",
10 Eds. J. Kucharczyk, et al., CRC Press Inc., Boca Raton, Florida, USA (1991), pages 177-203, especially page 188. See also, R. J. Gralla, et al., Cancer Treatment Reports, 68(1), 163-172 (1984).

The preferred class of antineoplastic agents is the taxanes and the preferred antineoplastic agent is paclitaxel.

15 The compounds of the instant invention may also be co-administered with antisense oligonucleotides which are specifically hybridizable with RNA or DNA deriving from human *ras* gene. Such antisense oligonucleotides are described in U.S. Patent No. 5,576,208 and PCT Publication No. WO 99/22772. The instant compounds are particularly useful when co-administered with the antisense oligo-
20 nucleotide comprising the amino acid sequence of SEQ.ID.NO: 2 of U.S. Patent No. 5,576,208.

Certain compounds of the instant invention may exhibit very low plasma concentrations and significant inter-individual variation in the plasma levels of the compound. It is believed that very low plasma concentrations and high
25 intersubject variability achieved following administration of certain prenyl-protein transferase inhibitors to mammals may be due to extensive metabolism by cytochrome P450 enzymes prior to entry of drug into the systemic circulation. Prenyl-protein transferase inhibitors may be metabolized by cytochrome P450 enzyme systems, such as CYP3A4, CYP2D6, CYP2C9, CYP2C19 or other
30 cytochrome P450 isoform. If a compound of the instant invention demonstrates an affinity for one or more of the cytochrome P450 enzyme systems, another compound with a higher affinity for the P450 enzyme(s) involved in metabolism should be administered concomitantly. Examples of compounds that have a comparatively very high affinity for CYP3A4, CYP2D6, CYP2C9, CYP2C19 or other P450 isoform
35 include, but are not limited to, piperonyl butoxide, troleandomycin, erythromycin,

proadifen, isoniazid, allylisopropylacetamide, ethinylestradiol, chloramphenicol, 2-ethynylnaphthalene and the like. Such a high affinity compound, when employed in combination with a compound of formula A, may reduce the inter-individual variation and increase the plasma concentration of a compound of formula A to a level having
5 substantial therapeutic activity by inhibiting the metabolism of the compound of formula A. Additionally, inhibiting the metabolism of a compound of the instant invention prolongs the pharmacokinetic half-life, and thus the pharmacodynamic effect, of the compound.

A compound of the present invention may be employed in conjunction
10 with antiemetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT₃ receptor antagonists, such
15 as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, or a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712. For the treatment or prevention of emesis, conjunctive therapy with a
20 neurokinin-1 receptor antagonist, a 5HT₃ receptor antagonist and a corticosteroid is preferred.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926,
25 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152,
30 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165,
35 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023,

93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 5 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 10 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689.

The preparation of such compounds is fully described in the aforementioned patents and publications.

15 A particularly preferred neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is 2-(R)-(1-(R)-(3,5-bis (trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

20 For the treatment of cancer, it may be desirable to employ a compound of the present invention in conjunction with another pharmacologically active agent(s). A compound of the present invention and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination. For example, the present compound may employed directly in combination with the other active agent(s), or it may be administered prior, concurrent or 25 subsequent to the administration of the other active agent(s). In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

30 For example, a compound of the present invention may be presented together with another therapeutic agent in a combined preparation, such as with an antiemetic agent for simultaneous, separate, or sequential use in the relief of emesis associated with employing a compound of the present invention and radiation therapy. Such combined preparations may be, for example, in the form of a twin pack. A preferred combination comprises a compound of the present invention with antiemetic 35 agents, as described above.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with the instant inhibitor of prenyl-protein transferase alone to treat cancer.

5 Additionally, compounds of the instant invention may also be useful as radiation sensitizers, as described in WO 97/38697, published on October 23, 1997, and herein incorporated by reference.

 The instant compounds may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth
10 factor receptors to nuclear signals initiating cellular proliferation. Thus, the instant compounds may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of the activity of farnesyl-protein transferase or in combination with a compound which has Raf antagonist activity. The instant compounds may also be co-administered with compounds that are selective inhibitors of geranylgeranyl
15 protein transferase.

 In particular, if the compound of the instant invention is a selective inhibitor of farnesyl-protein transferase, co-administration with a compound(s) that is a selective inhibitor of geranylgeranyl protein transferase may provide an improved therapeutic effect.

20 In particular, the compounds disclosed in the following patents and publications may be useful as farnesyl pyrophosphate-competitive inhibitor component of the instant composition: U.S. Serial Nos. 08/254,228 and 08/435,047. Those patents and publications are incorporated herein by reference.

 In practicing methods of this invention, which comprise administering,
25 simultaneously or sequentially or in any order, two or more of a protein substrate-competitive inhibitor and a farnesyl pyrophosphate-competitive inhibitor, such administration can be orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration. It is preferred that such administration be orally. It is more preferred that such
30 administration be orally and simultaneously. When the protein substrate-competitive inhibitor and farnesyl pyrophosphate-competitive inhibitor are administered sequentially, the administration of each can be by the same method or by different methods.

 The instant compounds may also be useful in combination with

an integrin antagonist for the treatment of cancer, as described in U.S. Serial No. 09/055,487, filed April 6, 1998, and WO 98/44797, published on October 15, 1998, which are incorporated herein by reference.

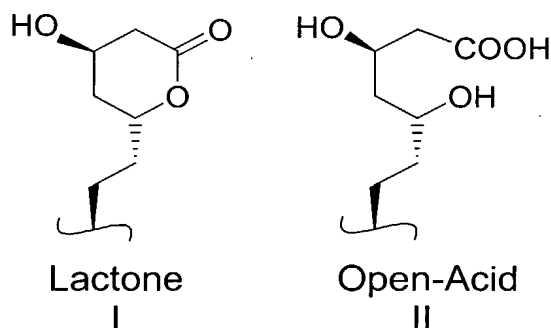
As used herein the term an integrin antagonist refers to compounds
5 which selectively antagonize, inhibit or counteract binding of a physiological ligand to an integrin(s) that is involved in the regulation of angiogenesis, or in the growth and invasiveness of tumor cells. In particular, the term refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v \beta 3$ integrin, which selectively antagonize, inhibit or counteract binding of a
10 physiological ligand to the $\alpha v \beta 5$ integrin, which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha v \beta 3$ integrin and the $\alpha v \beta 5$ integrin, or which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha 1 \beta 1$, $\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$ integrins. The term also refers to antagonists
15 of any combination of $\alpha v \beta 3$ integrin, $\alpha v \beta 5$ integrin, $\alpha 1 \beta 1$, $\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$ integrins. The instant compounds may also be useful with other agents that inhibit angiogenesis and thereby inhibit the growth and invasiveness of tumor cells, including, but not limited to angiostatin and endostatin.

The instant compounds may also be useful in combination with an
20 inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) for the treatment of cancer. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pages 30-33. The terms "HMG-CoA reductase inhibitor" and
25 "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US Patent No. 4,231,938; 4,294,926; 4,319,039), simvastatin (ZOCOR®; see US Patent No. 4,444,784; 4,820,850; 4,916,239), pravastatin (PRAVACHOL®; see US Patent Nos. 4,346,227;
30 4,537,859; 4,410,629; 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see US Patent Nos. 5,354,772; 4,911,165; 4,929,437; 5,189,164; 5,118,853; 5,290,946; 5,356,896), atorvastatin (LIPITOR®; see US Patent Nos. 5,273,995; 4,681,893; 5,489,691; 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional

HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.

10



In HMG-CoA reductase inhibitor's where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanol-amine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl)aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate,

bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, 5 lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor 10 compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

Similarly, the instant compounds may be useful in combination 15 with agents that are effective in the treatment and prevention of NF-1, restenosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ 20 the combinations of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Combinations of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

The instant compounds may also be useful in combination with 25 prodrugs of antineoplastic agents. In particular, the instant compounds may be co-administered either concurrently or sequentially with a conjugate (termed a "PSA conjugate") which comprises an oligopeptide, that is selectively cleaved by enzymatically active prostate specific antigen (PSA), and an antineoplastic agent. Such co-administration will be particularly useful in the treatment of prostate cancer or other cancers which are characterized by the presence of enzymatically active PSA 30 in the immediate surrounding cancer cells, which is secreted by the cancer cells.

Compounds which are PSA conjugates and are therefore useful in such 35 a co-administration, and methods of synthesis thereof, can be found in the following patents, pending patent applications and publications which are herein incorporated by reference:

U.S. Patent No. 5,599,686, granted on Feb. 4, 1997;

WO 96/00503 (January 11, 1996); USSN 08/404,833, filed on March 15, 1995;
USSN 08/468,161, filed on June 6, 1995;

5

U.S. Patent No. 5,866,679, granted on February 2, 1999;

WO 98/10651 (March 19, 1998); USSN 08/926,412, filed on September 9, 1997;

10 WO 98/18493 (May 7, 1998); USSN 08/950,805, filed on October 14, 1997;

WO 99/02175 (January 21, 1999); USSN 09/112,656, filed on July 9, 1998; and

WO 99/28345 (June 10, 1999); USSN 09/193,365, filed on November 17, 1998.

15

Compounds which are described as prodrugs wherein the active therapeutic agent is released by the action of enzymatically active PSA and therefore may be useful in such a co-administration, and methods of synthesis thereof, can be found in the following patents, pending patent applications and publications, which
20 are herein incorporated by reference: WO 98/52966 (November 26, 1998).

All patents, publications and pending patent applications identified are herein incorporated by reference.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested
25 may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period
30 of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant
35 invention relative to the presence of the unchanged substrate in the assay containing

the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a K_i substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

(*R*)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile hydrochloride

Step A: 4-(Hydroxymethyl)-1-(triphenylmethyl)imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in dry DMF (250 mL) at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenyl-

methane (76.1 g, 273 mmol) in DMF (500 mL) was added dropwise. The reaction mixture was stirred for 20 hrs, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid.

5

Step B: 4-(Acetoxymethyl)-1-(triphenylmethyl)imidazole
4-(Hydroxymethyl)-1-(triphenylmethyl)imidazole, as described in Step A above, (88.5 g, 260 mmol) was suspended in pyridine (500 mL). Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hrs during which it became homogeneous. The solution was poured into EtOAc, washed sequentially with water, 5% aqueous HCl solution, saturated aqueous NaHCO₃ solution, and brine. The organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to provide the ester as a white powder.

10

Step C: 5-(Acetoxymethyl)-1-(4-cyanobenzyl)imidazole hydrobromide
A solution of 4-(acetoxymethyl)-1-(triphenylmethyl) imidazole, as described in Step B above, (85.8 g, 225 mmol) and 4-cyanobenzyl bromide (50.1 g, 232 mmol) in EtOAc (500mL) was stirred at 60°C for 20 hrs, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume of 200 mL, reheated at 60°C for 2 hrs, cooled to room temperature, and filtered again. This filtrate was concentrated *in vacuo* to a volume of 100 mL, reheated at 60 °C for another 2 hrs, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in methanol (500mL), and warmed to 60°C. After 2 hrs, the solution was concentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product as a white solid.

20

25

Step D: 1-(4-Cyanobenzyl)-5-(hydroxymethyl)imidazole
To a solution of 5-(acetoxymethyl)-1-(4-cyanobenzyl)-imidazole hydrobromide, as described in Step C above, (50.4 g, 150 mmol) in 3:1 THF/water (1.5 L) at 0°C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After 1 hr, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, saturated aqueous NaHCO₃ and brine. The solution was then dried

35

(Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid.

Step E: 1-(4-Cyanobenzyl)-5-imidazolecarboxaldehyde

5 To a solution of 1-(4-cyanobenzyl)-5-(hydroxymethyl) imidazole, as described above in Step D, (21.5 g, 101 mmol) in DMSO (500 mL) at room temperature was added triethylamine (56 mL, 402 mmol), then SO₃-pyridine complex (40.5 g, 254 mmol). After 45 min, the reaction was poured into EtOAc (3 L), washed with water (4 × 800 mL), then brine (800 mL), dried (Na₂SO₄), and concentrated *in*
10 *vacuo* to provide the aldehyde as a white powder.

Step F: (R)-2-(tert-Butoxycarbonylamino)-4-(methylmercapto)-
N-phenylbutyramide

15 To (R)-N-(tert-butoxycarbonyl)methionine (589 mg, 2.36 mmol) in dry CH₂Cl₂ (5 mL) under argon were added PYBOP (1.23 g, 2.36 mmol), aniline (196 µL, 2.14 mmol), and N,N-diisopropylethylamine (655 µL, 3.76 mmol). The reaction mixture was stirred for 1 hr, then quenched with 10% citric acid (20 mL) and extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash
20 column chromatography on silica, eluting with hexane - 15% ethyl acetate to yield the product as a white solid.

Step G: (R)-2-(tert-Butoxycarbonylamino)-4-(dimethylsulfonium)-
N-phenylbutyramide iodide

25 (R)-2-(tert-Butoxycarbonylamino)-4-(methylmercapto)-N-phenylbutyramide, as described above in Step F, (650 mg, 2.00 mmol) was dissolved in iodomethane (3 mL, 48.0 mmol) and the solution was stirred under argon for 18 hrs. The iodomethane was removed by distillation under reduced pressure to give the sulfonium salt as a white solid.

30

Step H: (R)-3-(tert-Butoxycarbonylamino)-2-oxo-1-phenylpyrrolidine
 (R)-2-(tert-Butoxycarbonylamino)-4-(dimethylsulfonium)-N-
phenylbutyramide iodide, as described above in Step G, (930 mg, 2.0 mmol) was stirred in dry THF (40 mL), under argon, at 0°C and lithium bis(trimethylsilyl)amide

(1.0 M in THF, 2.0 mL, 2.0 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 2 h, then quenched with saturated aqueous NH₄Cl (5 mL) and most of the THF was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (10 mL) and CH₂Cl₂ (20 mL).

- 5 The aqueous layer was extracted further with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane -20% ethyl acetate to yield the above-titled pyrrolidinone as a white solid.

10 Step I: (R)-3-Amino-2-oxo-1-phenylpyrrolidine hydrochloride

A solution of (R)-3-(*tert*-butoxycarbonylamino)-2-oxo-1-phenylpyrrolidine, as described above in Step H, (490 mg, 1.8 mmol) in EtOAc (40 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the above-titled amine hydrochloride as a pale solid.

15

Step J: (R)- 4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile hydrochloride

- (R)-3-Amino-2-oxo-1-phenylpyrrolidine, as described above in Step I, (100 mg, 0.57 mmol), 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde, as described above in Step E, (132 mg, 0.62 mmol), and acetic acid (98 µL, 1.71 mmol) were stirred in MeOH (2 mL) for 1 hr then NaCNBH₃ (47 mg, 0.74 mmol) was added. Stirring was continued for 1 hr, then the reaction was quenched with saturated aqueous NaHCO₃ (2 mL) and most of the MeOH was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (5 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ - 2% MeOH - 0.2% NH₄OH, to yield the desired product which was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.
- 20
25
30

Elemental analysis calculated for C₂₂H₂₁N₅O•1.4 HCl•0.85 H₂O:

C: 60.35; H: 5.55; N: 16.00

Found: C: 60.39; H: 5.54; N: 15.90

35 FAB MS: 372 (MH⁺).

EXAMPLE 1A(S)-3-Amino-2-oxo-1-phenylpyrrolidine hydrochloride

5 Following the procedures described in Example 1, Steps F-I, but using
(S)-N-(*tert*-butoxycarbonyl)methionine in place of (R)-N-(*tert*-butoxycarbonyl)
methionine in Step F, the above-title compound was obtained.

EXAMPLE 1B

10

(R)-3-Amino-1-benzyl-2-oxopyrrolidine hydrochloride

 Following the procedures described in Example 1, Steps F-I, but using
benzylamine in place of aniline in Step F, the above-title compound was obtained.

15

EXAMPLE 1C(S)-3-Amino-1-benzyl-2-oxopyrrolidine hydrochloride

 Following the procedures described in Example 1, Steps F-I, but using
benzylamine in place of aniline and (S)-N-(*tert*-butoxycarbonyl) methionine in place
20 of (R)-N-(*tert*-butoxycarbonyl) methionine in Step F, the above-title compound was
obtained.

EXAMPLE 1D

25

(R)-1-Benzyl-3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidine

 Following the procedures described in Example 1, Steps F-H, but using
benzylamine in place of aniline in Step F, the above-title compound was obtained.

EXAMPLE 1E

30

(S)-1-Benzyl-3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidine

 Following the procedures described in Example 1, Steps F-H, but using
benzylamine in place of aniline and (S)-N-(*tert*-butoxycarbonyl) methionine in place
of (R)-N-(*tert*-butoxycarbonyl)methionine in Step F, the above-title compound was
35 obtained.

EXAMPLE 1F(R)-3-Amino-2-oxo-1-phenethylpyrrolidine hydrochloride

5 Following the procedures described in Example 1, Steps F-I, but using phenethylamine in place of aniline in Step F, the above-title compound was obtained.

EXAMPLE 1G(S)-3-Amino-2-oxo-1-phenethylpyrrolidine hydrochloride

10 Following the procedures described in Example 1, Steps F-I, but using phenethylamine in place of aniline and (S)-N-(tert-butoxycarbonyl) methionine in place of (R)-N-(tert-butoxycarbonyl) methionine in Step F, the above-title compound was obtained.

15

EXAMPLE 1H(R)-3-Amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride

20 Following the procedures described in Example 1, Steps F-I, but using 3-chlorobenzylamine in place of aniline in Step F, the above-title compound was obtained.

EXAMPLE 1I(S)-3-Amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride

25 Following the procedures described in Example 1, Steps F-I, but using 3-chlorobenzylamine in place of aniline and (S)-N-(tert-butoxycarbonyl)methionine in place of (R)-N-(tert-butoxycarbonyl) methionine in Step F, the above-title compound was obtained.

30

EXAMPLE 2(S)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile hydrochloride

35 Following the procedures described in Example 1, but using (S)-N-(tert-butoxycarbonyl)methionine in place of (R)-N-(tert-butoxycarbonyl)methionine

in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{22}H_{21}N_5O \cdot 1.7 HCl \cdot 1.7 H_2O \cdot 0.2 EtOAc$:

C: 56.96; H: 5.79; N: 14.57

5 Found: C: 56.93; H: 5.67; N: 14.54

FAB MS: 372 (MH^+).

EXAMPLE 3

10 (R)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

Following the procedures described in Example 1, but using
benzylamine in place of aniline in Step F, the above-title compound was obtained.

15 Elemental analysis calculated for $C_{23}H_{23}N_5O \cdot 1.6 HCl \cdot 0.7 H_2O \cdot 0.35 CH_3CN$:

C: 60.46; H: 5.79; N: 15.92

Found: C: 60.40; H: 5.79; N: 15.91

FAB MS: 386 (MH^+).

EXAMPLE 4

20 (S)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

25 Following the procedures described in Example 1, but using
benzylamine in place of aniline and (S)-N-(tert-butoxycarbonyl) methionine in place
of (R)-N-(tert-butoxycarbonyl) methionine in Step F, the above-title compound was
obtained.

Elemental analysis calculated for $C_{23}H_{23}N_5O \cdot 1.8 HCl \cdot 1.5 H_2O$:

30 C: 57.77; H: 5.86; N: 14.69

Found: C: 57.77; H: 5.85; N: 14.77

FAB MS: 386 (MH^+).

EXAMPLE 5

35

(*R*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 1, but using 2-chloroaniline in place of aniline in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{22}H_{20}ClN_5O \cdot 2 HCl \cdot 0.75 H_2O \cdot 0.2 CH_2Cl_2$:

C: 52.35; H: 4.73; N: 13.75

Found: C: 52.33; H: 4.73; N: 13.80

FAB MS: 406 (MH^+).

EXAMPLE 6

(*S*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 1, but using 2-chloroaniline in place of aniline and (*S*)-*N*-(*tert*-butoxycarbonyl) methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl) methionine in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{22}H_{20}ClN_5O \cdot 2 HCl \cdot 1.2 H_2O \cdot 0.1 CH_2Cl_2$:

C: 52.15; H: 4.87; N: 13.76

Found: C: 52.15; H: 4.84; N: 13.93

FAB MS: 406 (MH^+).

EXAMPLE 7

(*S*)-4-(5-{[1-(3-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 1, but using 3-chloroaniline in place of aniline and (*S*)-*N*-(*tert*-butoxycarbonyl) methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl) methionine in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{22}H_{20}ClN_5O \cdot 2 HCl \cdot 0.15 EtOAc \cdot 0.3 CH_2Cl_2$:

C: 53.14; H: 4.64; N: 13.53

Found: C: 53.11; H: 4.89; N: 13.60
FAB MS: 406 (MH⁺).

EXAMPLE 8

5

(R)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 1, but using 4-chloroaniline in place of aniline in Step F, the above-title compound was obtained.

10

Elemental analysis calculated for C₂₂H₂₀ClN₅O•2 HCl•1.3 H₂O:

C: 52.61; H: 4.94; N: 13.95

Found: C: 52.60; H: 4.76; N: 14.02

FAB MS: 406 (MH⁺).

15

EXAMPLE 9

(S)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

20

Following the procedures described in Example 1, but using 4-chloroaniline in place of aniline and (S)-N-(tert-butoxycarbonyl) methionine in place of (R)-N-(tert-butoxycarbonyl) methionine in Step F, the above-title compound was obtained.

25

Elemental analysis calculated for C₂₂H₂₀ClN₅O•2 HCl•1.05 H₂O:

C: 53.09; H: 4.88; N: 14.07

Found: C: 53.05; H: 4.69; N: 14.37

FAB MS: 406 (MH⁺).

30

EXAMPLE 10

(S)-4-(5-{[1-(2-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

35

Following the procedures described in Example 1, but using 2-chlorobenzylamine in place of aniline and (S)-N-(tert-butoxycarbonyl) methionine in

place of (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{23}H_{22}ClN_5O \cdot 2 HCl \cdot 0.15 H_2O \cdot 0.4 CH_2Cl_2$:

5 C: 53.07; H: 4.78; N: 13.32

Found: C: 53.09; H: 4.68; N: 13.30

FAB MS: 420 (MH^+).

EXAMPLE 11

10

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

15

Following the procedures described in Example 1, but using 3-chlorobenzylamine in place of aniline in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{23}H_{22}ClN_5O \cdot 2 HCl \cdot 0.55 H_2O \cdot 0.3 CH_2Cl_2$:

C: 52.98; H: 4.90; N: 13.26

Found: C: 52.97; H: 4.89; N: 13.32

20 FAB MS: 420 (MH^+).

EXAMPLE 12

25

(*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

30

Following the procedures described in Example 1, but using 3-chlorobenzylamine in place of aniline and (*S*)-*N*-(*tert*-butoxycarbonyl) methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{23}H_{22}ClN_5O \cdot 2 HCl \cdot 0.65 H_2O$:

C: 54.75; H: 5.05; N: 13.88

Found: C: 54.75; H: 5.17; N: 14.00

FAB MS: 420 (MH^+).

35

EXAMPLE 13

(*S*)-4-(5-{[1-(4-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

5 Following the procedures described in Example 1, but using 4-chlorobenzylamine in place of aniline and (*S*)-*N*-(*tert*-butoxycarbonyl) methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in Step F, the above-title compound was obtained.

10 Elemental analysis calculated for $C_{23}H_{22}ClN_5O \cdot 2 HCl \cdot 0.35 CHCl_3 \cdot 0.05 EtOAc$:

C: 52.47; H: 4.63; N: 12.99

Found: C: 52.39; H: 5.00; N: 13.32

FAB MS: 420 (MH^+).

15

EXAMPLE 14

(*R*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

20 Following the procedures described in Example 1, but using phenethylamine in place of aniline in Step F, the above-title compound was obtained.

Elemental analysis calculated for $C_{24}H_{25}N_5O \cdot 2 HCl \cdot 0.65 H_2O$:

C: 59.54; H: 5.89; N: 14.47

Found: C: 59.48; H: 6.04; N: 14.53

25 FAB MS: 400 (MH^+).

EXAMPLE 15

(*S*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

30 Following the procedures described in Example 1, but using phenethylamine in place of aniline and (*S*)-*N*-(*tert*-butoxycarbonyl) methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in Step F, the above-title compound was obtained.

35

Elemental analysis calculated for $C_{24}H_{25}N_5O \cdot 2 HCl \cdot 0.85 H_2O$:

C: 59.10; H: 5.93; N: 14.36

Found: C: 59.08; H: 5.85; N: 14.60

FAB MS: 400 (MH^+).

5

EXAMPLE 16

(*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)
acetamide hydrochloride

10

Step A: Methyl(imidazol-4-yl)acetate hydrochloride

A solution of 4-imidazoleacetic acid hydrochloride (4.00 g, 24.6 mmol) in MeOH (100 mL) was saturated with HCl (g). Trimethyl orthoformate (10 mL, 91 mmol) was added and the mixture was allowed to stand at ambient temperature for 18 hrs, then concentrated to dryness *in vacuo* to afford the titled ester as a white solid.

15

Step B: Methyl [1-(triphenylmethyl)-1*H*-imidazol-4-yl]acetate

To a solution of methyl (imidazol-4-yl)acetate hydrochloride, as described above in Step A, (4.30 g, 24.3 mmol) in dry DMF (50 mL) were added triethylamine (7.45 mL, 53.5 mmol), then triphenylmethyl bromide (8.64 g, 26.7 mmol). The mixture was stirred at ambient temperature for 18 hrs, then partitioned between H₂O (250 mL) and EtOAc (250 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate, to yield the product as a pale solid.

20

25

Step C: Methyl [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate hydrobromide

A mixture of methyl [1-(triphenylmethyl)-1*H*-imidazol-4-yl]acetate, as described above in Step B, (3.33 g, 8.71 mmol) and 4-cyanobenzyl bromide (1.71 g, 8.71 mmol) in acetonitrile (30 mL) was heated to 50°C for 2 hrs. The mixture was allowed to cool, and the solid collected by filtration. The acetonitrile filtrate was concentrated *in vacuo* to a volume of approximately 10 mL and then reheated to 50°C for 2 hrs, cooled, and the solid removed by filtration. The two crops of precipitated imidazolium salts were combined in MeOH (100 mL) and the solution was heated to

30

35

reflux for 30 min, then concentrated *in vacuo* to a volume of approximately 5 mL. EtOAc was added, and the titled product was crystallized and then collected by filtration.

- 5 Step D: Lithium [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate
 Methyl [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate hydrobromide,
as described above in Step C, (1.36 g, 4.05 mmol) was dissolved in THF (26 mL) and
H₂O (4.5 mL). 1.0 N aqueous lithium hydroxide (4.45 mL, 4.45 mmol) was added
and the resulting mixture was stirred at ambient temperature for 18 hrs, then adjusted
10 to pH 7 with 1.0 N aqueous HCl and concentrated to dryness *in vacuo* to give the
titled lithium salt.

- Step E: (*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)acetamide hydrochloride
15 Lithium [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate, as described
above in Step D, (93 mg, 0.37 mmol) was dissolved in CH₂Cl₂ (1 mL) and DMF
(1 mL). PYBOP (195 mg, 0.37 mmol), (*R*)-3-amino-2-oxo-1-phenylpyrrolidine,
as described in Example 1, Step I, (60 mg, 0.34 mmol), and diisopropylethylamine
(208 mL, 1.19 mmol) were added and the mixture was stirred at ambient temperature
20 for 18 hrs. The solvents were removed under reduced pressure and the residue was
partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL). The
aqueous layer was extracted further with CH₂Cl₂ (3 × 5 mL). The combined organic
extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude
product was purified by flash column chromatography on silica, eluting with CH₂Cl₂
25 -8% MeOH - 0.5% NH₄OH to yield the titled product, which was converted to the
hydrochloride salt by treatment with aqueous HCl in acetonitrile.

Elemental analysis calculated for C₂₃H₂₁N₅O₂•0.7 HCl•1.8 H₂O:

- C: 60.39; H: 5.58; N: 15.31
30 Found: C: 60.41; H: 5.59; N: 15.62
 FAB MS: 400 (MH⁺).

EXAMPLE 17

- 35 (*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)

acetamide hydrochloride

Following the procedures described in Example 16, but using (*S*)-3-amino-2-oxo-1-phenylpyrrolidine (as described in Example 1A) in place of (*R*)-3-amino-2-oxo-1-phenylpyrrolidine in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{23}H_{21}N_5O_2 \cdot 1.3 HCl \cdot 2.5 H_2O \cdot 0.25 EtOAc$:

C: 56.18; H: 5.74; N: 13.65

Found: C: 56.17; H: 5.89; N: 13.63

FAB MS: 400 (MH^+).

EXAMPLE 18

(*R*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]
acetamide hydrochloride

Following the procedures described in Example 16, but using (*R*)-3-amino-1-benzyl-2-oxopyrrolidine (as described in Example 1B) in place of (*R*)-3-amino-2-oxo-1-phenylpyrrolidine in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{24}H_{23}N_5O_2 \cdot 0.6 HCl \cdot H_2O$:

C: 63.58; H: 5.69; N: 15.45

Found: C: 63.61; H: 5.68; N: 15.40

FAB MS: 414 (MH^+).

EXAMPLE 19

(*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]
acetamide hydrochloride

Following the procedures described in Example 16, but using (*S*)-3-amino-1-benzyl-2-oxopyrrolidine (as described in Example 1C) in place of (*R*)-3-amino-2-oxo-1-phenylpyrrolidine in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{24}H_{23}N_5O_2 \cdot 0.8 HCl \cdot H_2O$:

C: 62.57; H: 5.65; N: 15.20

Found: C: 62.61; H: 5.66; N: 15.04

FAB MS: 414 (MH^+).

EXAMPLE 20

5 (R)-N-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1H-imidazol-5-yl]-N-methylacetamide hydrochloride

Step A: (R)-1-Benzyl-3-[(tert-butoxycarbonyl)methylamino]-2-oxopyrrolidine

To a stirred solution of (R)-1-benzyl-3-(tert-butoxycarbonyl-amino)-2-oxopyrrolidine (as described in Example 1D) (200 mg, 0.69 mmol) in dry THF (3 mL) at 0°C was added lithium bis(trimethylsilyl) amide (1.0 M in THF, 0.69 mL, 0.69 mmol) dropwise. The resulting solution was stirred for 2 hrs at 0°C, then iodomethane (47 mL, 0.75 mmol) was added and stirring was continued at 0°C for 4 hrs. The reaction was quenched by addition of saturated aqueous NaHCO₃ (3 mL) and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic
10 extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by semi-preparative HPLC using a Vydac C18 reversed phase column and eluting with a gradient of 95/5 to 0/100 A/B; A = H₂O-0.1% TFA, B = CH₃CN-0.1% TFA. The pure fractions were collected and extracted with CH₂Cl₂ (15 mL), and the CH₂Cl₂ layer was dried over MgSO₄, filtered, and concentrated *in vacuo*
15 to give the titled product as a colorless oil.

Step B: (R)-1-Benzyl-3-(methylamino)-2-oxopyrrolidine-hydrochloride

A solution of (R)-1-Benzyl-3-[N-(tert-butoxycarbonyl)-N-methylamino]-2-oxopyrrolidine, as described above in Step A, (100 mg, 0.33
25 mmol) in EtOAc (3 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine hydrochloride as a pale solid.

30 Step C: (R)-N-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1H-imidazol-5-yl]-N-methylacetamide hydrochloride

Lithium [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetate, as described in Example 16, Step D, (116 mg, 0.47 mmol), (R)-1-benzyl-3-(methylamino)-2-oxopyrrolidine, as described above in Step B, (80 mg, 0.39 mmol), EDC (113 mg, 0.59 mmol), 1-hydroxybenzotriazole hydrate (80 mg, 0.59 mmol), and N,N-diisopropylethylamine (103 mL, 0.59 mmol) were combined in DMF (1 mL) and the
35

- mixture was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (3 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 3 mL). The combined organic extracts were dried over MgSO₄,
5 filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ - 4% MeOH - 0.3% NH₄OH to yield the titled product, which was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.
- 10 Elemental analysis calculated for C₂₅H₂₅N₅O₂•1.4 HCl•0.05 H₂O:
C: 62.86; H: 5.58; N: 14.66
Found: C: 62.88; H: 5.57; N: 14.41
FAB MS: 428 (MH⁺).

15 EXAMPLE 21

(*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-methylacetamide hydrochloride

- 20 Following the procedures described in Example 20, but using (*S*)-1-benzyl-3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidine (as described in Example 1E) in place of (*R*)-1-benzyl-3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidine in Step A, the above-titled compound was obtained.

- Elemental analysis calculated for C₂₅H₂₅N₅O₂•1.3 HCl•0.7 H₂O:
25 C: 61.82; H: 5.74; N: 14.42
Found: C: 61.86; H: 5.73; N: 14.43
FAB MS: 428 (MH⁺).

EXAMPLE 22

(*R*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}-benzonitrile hydrochloride

- 5 (*R*)-3-Amino-1-benzylpyrrolidine, (100 mg, 0.57 mmol), 1-(4-cyanobenzyl)-5-imidazolecarbox-aldehyde, as described in Example 1, Step E, (126 mg, 0.60 mmol), and acetic acid (130 mL, 2.27 mmol) were stirred in MeOH (1 mL) for 1 hr then NaCNBH₃ (43 mg, 0.68 mmol) was added. Stirring was continued for 1 hr, then the reaction was quenched with saturated aqueous NaHCO₃ (2 mL) and
- 10 most of the MeOH was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (5 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 5mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂
- 15 -3% MeOH - 0.3% NH₄OH, to yield the desired product which was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.

Elemental analysis calculated for C₂₃H₂₅N₅•2 HCl•0.3 H₂O•0.7 EtOAc:

- 20 Found: C: 60.58; H: 6.54; N: 13.69
C: 60.60; H: 6.24; N: 13.72
FAB MS: 372 (MH⁺).

EXAMPLE 23

- 25 (*S*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}-benzonitrile hydrochloride
-

- Following the procedures described in Example 22, but using (*S*)-3-amino-1-benzylpyrrolidine in place of (*R*)-3-amino-1-benzylpyrrolidine, the above-titled compound was obtained.

- 30 Elemental analysis calculated for C₂₃H₂₅N₅•1.5 HCl•0.5 H₂O•0.3 EtOAc:
C: 64.09; H: 6.45; N: 15.44
Found: C: 64.05; H: 6.33; N: 15.42
FAB MS: 372 (MH⁺).

35

EXAMPLE 24

(S)-4-(5-{[Benzyl(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

- 5 (S)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride (as described in Example 4) (50 mg, 0.13 mmol), benzaldehyde (21 mg, 0.19 mmol), and acetic acid (30 mL, 0.52 mmol) were stirred in MeOH (0.5 mL) for 1 hr then NaCNBH₃ (11 mg, 0.18 mmol) was added. Stirring was continued for 3 hrs, then the reaction was quenched with saturated
- 10 aqueous NaHCO₃ (1 mL) and most of the MeOH was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (2 mL) and EtOAc (2 mL). The aqueous layer was extracted further with EtOAc (2 × 2mL).
- The combined organic extracts were dried over MgSO₄, filtered, and concentrated
- 15 *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ - 2% MeOH - 0.2% NH₄OH, to yield the desired product which was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.

Elemental analysis calculated for C₃₀H₂₉N₅O•1.6 HCl•H₂O:

- 20 C: 65.28; H: 5.95; N: 12.69
Found: C: 65.34; H: 5.96; N: 12.65
FAB MS: 476 (MH⁺).

EXAMPLE 25

- 25 (S)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)phenethylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride
-

- Following the procedures described in Example 24, but using phenylacetaldehyde in place of benzaldehyde, the above-titled compound was
- 30 obtained.

Elemental analysis calculated for C₃₁H₃₁N₅O•1.6 HCl•1.6 H₂O:

- C: 64.65; H: 6.25; N: 12.16
Found: C: 64.59; H: 6.25; N: 12.16
35 FAB MS: 490 (MH⁺).

EXAMPLE 26

(S)-4-(5-([(1-Benzyl-2-oxopyrrolidin-3-yl)(3-phenylpropyl)amino]-methyl)imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 24, but using 3-phenylpropionaldehyde in place of benzaldehyde, the above-titled compound was obtained.

10 Elemental analysis calculated for $C_{32}H_{33}N_5O \cdot 1.4 HCl \cdot 1.7 H_2O$:

C: 65.86; H: 6.52; N: 12.00

Found: C: 65.91; H: 6.53; N: 11.93

FAB MS: 504 (MH^+).

EXAMPLE 27

(S)-4-(5-[[(1-Benzyl-2-oxopyrrolidin-3-yl)(4-phenylbutyl)amino]-methyl]imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 24, but using 4-phenylbutyraldehyde in place of benzaldehyde, the above-titled compound was obtained.

Elemental analysis calculated for $C_{33}H_{35}N_5O \cdot 1.5 HCl \cdot 1.5 H_2O$:

C: 66.02; H: 6.62; N: 11.67

25 Found: C: 65.98; H: 6.63; N: 11.69

FAB MS: 518 (MH^+).

EXAMPLE 28

(*R*)-4-(5-[(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino]methyl)imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 24, but using propionaldehyde in place of benzaldehyde and (*R*)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride (as described in Example 3) in place of (*S*)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino)methyl]

imidazol-1-ylmethyl}benzonitrile, the above-titled compound was obtained.

Elemental analysis calculated for $C_{26}H_{29}N_5O \cdot 2 HCl \cdot 0.65 H_2O$:

C: 60.97; H: 6.36; N: 13.67

5 Found: C: 60.96; H: 6.35; N: 13.45

FAB MS: 428 (MH^+).

EXAMPLE 29

10 (*S*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 24, but using propionaldehyde in place of benzaldehyde, the above-titled compound was obtained.

15 Elemental analysis calculated for $C_{26}H_{29}N_5O \cdot 2 HCl \cdot 0.55 H_2O \cdot 0.25 EtOAc$:

C: 60.91; H: 6.46; N: 13.16

Found: C: 60.87; H: 6.30; N: 13.16

FAB MS: 428 (MH^+).

20

EXAMPLE 30

(*R*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

25 Following the procedures described in Example 24, but using butyraldehyde in place of benzaldehyde and (*R*)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride (as described in Example 3) in place of (*S*)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile, the above-titled compound was obtained.

30 Elemental analysis calculated for $C_{27}H_{31}N_5O \cdot 1.8 HCl \cdot H_2O \cdot 0.4 CH_3CN$:

C: 61.64; H: 6.70; N: 13.97

Found: C: 61.62; H: 6.69; N: 13.96

FAB MS: 442 (MH^+).

35

EXAMPLE 31

(S)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino}methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

5 Following the procedures described in Example 24, but using butyraldehyde in place of benzaldehyde, the above-titled compound was obtained.

Elemental analysis calculated for $C_{27}H_{31}N_5O \cdot 2.5 HCl \cdot 1.8 H_2O \cdot 0.4 CH_3CN$:

C: 57.50; H: 6.63; N: 13.03

Found: C: 57.54; H: 6.33; N: 13.01

10 FAB MS: 442 (MH^+).

EXAMPLE 32

15 (S)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-2-ylmethylamino}-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

 Following the procedures described in Example 24, but using 2-pyridinecarboxaldehyde in place of benzaldehyde, the above-titled compound was obtained.

20 Elemental analysis calculated for $C_{29}H_{28}N_6O \cdot 2.5 HCl \cdot 2.3 H_2O \cdot 0.35 CH_2Cl_2$:

C: 55.25; H: 5.64; N: 13.17

Found: C: 55.25; H: 5.67; N: 12.91

FAB MS: 477 (MH^+).

25 EXAMPLE 33

(S)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-3-ylmethylamino}-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

30 Following the procedures described in Example 24, but using 3-pyridinecarboxaldehyde in place of benzaldehyde, the above-titled compound was obtained.

Elemental analysis calculated for $C_{29}H_{28}N_6O \cdot 2.5 HCl \cdot 0.55 H_2O \cdot 0.55 CH_2Cl_2$:

C: 56.84; H: 5.28; N: 13.46

Found: C: 56.83; H: 5.28; N: 13.20

35 FAB MS: 477 (MH^+).

EXAMPLE 34

5 (S)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-4-ylmethylamino}-methyl}
imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 24, but using 4-pyridinecarboxaldehyde in place of benzaldehyde, the above-titled compound was obtained.

10 Elemental analysis calculated for $C_{29}H_{28}N_6O \cdot 2.5 HCl \cdot 1.3 H_2O \cdot 0.45 CH_2Cl_2$:

C: 56.20; H: 5.45; N: 13.35

Found: C: 56.19; H: 5.44; N: 13.32

FAB MS: 477 (MH^+).

15 EXAMPLE 35

(S)-4-(5-{{(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl}-imidazol-
1-ylmethyl)benzonitrile hydrochloride

20 Step A: 3-(tert-Butoxycarbonylamino)propionaldehyde

To a stirred solution of oxalyl chloride (0.32 mL, 3.7 mmol) in dry CH_2Cl_2 (5 mL) at $-70^\circ C$, under argon, was added dry DMSO (0.53 mL, 7.5 mmol) dropwise. The resulting mixture was stirred at $-70^\circ C$ for 10 min, then a solution of 3-(tert-butoxycarbonylamino)propanol (500 mg, 2.85 mmol) in CH_2Cl_2 (3 mL) was
25 added slowly. After stirring for an additional 15 min, triethylamine (2.0 mL, 14.3 mmol) was added and the mixture was allowed to warm to ambient temperature, then partitioned between hexane (20 mL) and H_2O (30 mL). The organic phase was further washed with saturated aqueous $NaHCO_3$ (20 mL) and then brine (20 mL), then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to obtain the crude aldehyde.

30

Step B: (S)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)(3-{tert-butoxycarbonyl-
amino}propyl)amino}methyl}imidazol-1-ylmethyl)benzonitrile

(S)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride (as described in Example 4) (90 mg, 0.23
35 mmol), 3-(tert-butoxycarbonylamino)propionaldehyde, as described above in Step A,

(81 mg, 0.47 mmol), and acetic acid (27 mL, 0.47 mmol) were stirred in MeOH (1 mL) for 1 hr then NaCNBH₃ (18 mg, 0.29 mmol) was added. Stirring was continued for 18 hrs, then most of the MeOH was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (5 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂-2% MeOH - 0.2% NH₄OH, to yield the desired product.

10 Step C: (S)-4-(5-{[(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

A solution (S)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)(3-{*tert*-butoxycarbonylamino}propyl)amino]methyl}imidazol-1-ylmethyl)-benzonitrile, as described above in Step B, (15 mg, 0.028 mmol) in EtOAc (5 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine hydrochloride as a white solid.

Elemental analysis calculated for C₂₆H₃₀N₆O•2.5 HCl•0.45 EtOAc•0.45 CH₂Cl₂:

C: 55.48; H: 6.10; N: 13.74

20 Found: C: 55.33; H: 6.09; N: 13.79

FAB MS: 443 (MH⁺).

EXAMPLE 36

25 (S)-4-(5-{[(2-Aminoethyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 35, but using 2-(*tert*-butoxycarbonylamino)ethanol in place of 3-(*tert*-butoxycarbonylamino)propanol in Step A, the above-titled compound was obtained.

30

Elemental analysis calculated for C₂₅H₂₈N₆O•2.5 HCl•1.8 H₂O:

C: 54.38; H: 6.23; N: 15.22

Found: C: 54.39; H: 6.08; N: 14.93

FAB MS: 429 (MH⁺).

35

EXAMPLE 37

(*S*)-4-(5-{[(4-Aminobutyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino]-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

- 5 Following the procedures described in Example 35, but using 4-(*tert*-butoxycarbonylamino)butanol in place of 3-(*tert*-butoxycarbonylamino)propanol in Step A, the above-titled compound was obtained.

Elemental analysis calculated for C₂₇H₃₂N₆O•2.5 HCl•2.5 H₂O:

10 C: 54.78; H: 6.71; N: 14.20

Found: C: 54.79; H: 6.45; N: 14.35

FAB MS: 457 (MH⁺).

EXAMPLE 38

15

(*R*)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

Step A: 4-[5-(2-Hydroxyethyl)imidazol-1-ylmethyl]benzonitrile

20

To a stirred solution of methyl [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate hydrobromide, as described in Example 16, Step C (1.44 g, 5.64 mmol) in methanol at 0°C was added sodium borohydride (0.96 g, 25.4 mmol) in one portion. After 3 hrs, saturated aqueous NH₄Cl (20 mL) was added, followed by saturated aqueous NaHCO₃ (20 mL), and the mixture was extracted with EtOAc (3 × 75 mL).
25 The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ - 5% MeOH, to yield the desired product.

Step B: Methanesulfonic acid 2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]ethyl ester

30

A solution of 4-[5-(2-hydroxyethyl)imidazol-1-ylmethyl]-benzonitrile, as described above in Step A, (250 mg, 1.10 mmol) in dry CH₂Cl₂ (35 mL) at 0°C, under argon, was treated with *N,N*-diisopropylethylamine (233 mL, 1.34 mmol) followed by methanesulfonyl chloride (103 mL, 1.33 mmol). The reaction mixture
35 was stirred at 0°C for 3 hrs, then quenched with saturated aqueous NaHCO₃ (25 mL)

and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo* to give the mesylate as a thick yellow oil.

- 5 Step C: (R)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]-
 imidazol-1-ylmethyl}benzonitrile hydrochloride
 Methanesulfonic acid 2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]ethyl
 ester, as described above in Step B, (173 mg, 0.57 mmol), (*R*)-3-amino-1-benzyl-
 2-oxopyrrolidine hydrochloride (as described in Example 1B) (80 mg, 0.42 mmol),
 10 sodium iodide (126 mg, 0.84 mmol), and *N,N*-diisopropylethylamine (110 mL,
 0.63 mmol) were combined in dry, degassed DMF (2 mL) and heated to 50°C, under
 argon, for 18 hrs. The reaction was quenched with saturated aqueous NaHCO₃ (2
 mL) and then concentrated under reduced pressure. The residue was partitioned
 between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (5 mL). The aqueous layer
 15 was extracted further with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were
 dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was
 purified by flash column chromatography on silica, eluting with a gradient of CHCl₃
 - 3% to 4% MeOH - 0.4% NH₄OH, to yield the desired product which was converted
 to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.

20 Elemental analysis calculated for C₂₄H₂₅N₅O•2.5 HCl•0.65 CH₃CN•0.85 PhCH₃:
 C: 62.29; H: 6.06; N: 13.14
 Found: C: 62.23; H: 6.05; N: 13.16
 FAB MS: 400 (MH⁺).

25

EXAMPLE 39

(S)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

- 30 Following the procedures described in Example 38, but using (*S*)-
 3-amino-1-benzyl-2-oxopyrrolidine hydrochloride (as described in Example 1C)
 in place of (*R*)-3-amino-1-benzyl-2-oxopyrrolidine hydrochloride in Step C, the
 above-titled compound was obtained.

35 Elemental analysis calculated for C₂₄H₂₅N₅O•2.5 HCl•0.2 H₂O•0.35 Et₂O:

C: 58.64; H: 6.08; N: 13.46
Found: C: 58.67; H: 6.08; N: 13.45
FAB MS: 400 (MH^+).

5

EXAMPLE 40

(R)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

Following the procedures described in Example 38, but using (R)-3-
10 amino-2-oxo-1-phenylpyrrolidine hydrochloride (as described in Example 1, Step I)
in place of (R)-3-amino-1-benzyl-2-oxopyrrolidine hydrochloride in Step C, the
above-title compound was obtained.

Elemental analysis calculated for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O} \cdot 2.3 \text{ HCl} \cdot 0.85 \text{ H}_2\text{O}$:
15 C: 57.00; H: 5.62; N: 14.45
Found: C: 56.93; H: 5.62; N: 14.45
FAB MS: 386 (MH^+).

EXAMPLE 41

20

(S)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

Following the procedures described in Example 38, but using (S)-
3-amino-2-oxo-1-phenylpyrrolidine hydrochloride (as described in Example 1A)
25 in place of (R)-3-amino-1-benzyl-2-oxopyrrolidine hydrochloride in Step C, the
above-title compound was obtained.

Elemental analysis calculated for $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O} \cdot 2.5 \text{ HCl} \cdot 1.2 \text{ H}_2\text{O}$:
C: 56.90; H: 5.72; N: 14.43
30 Found: C: 56.94; H: 5.72; N: 14.12
FAB MS: 386 (MH^+).

EXAMPLE 42

(*R*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

- Following the procedures described in Example 38, but using (*R*)-3-amino-2-oxo-1-phenethylpyrrolidine hydrochloride (as described in Example 1F) in place of (*R*)-3-amino-1-benzyl-2-oxopyrrolidine hydrochloride in Step C, the above-
- 5 title compound was obtained.

Elemental analysis calculated for $C_{25}H_{27}N_5O \cdot 2 HCl \cdot 1.5 H_2O \cdot 0.25 CH_2Cl_2$:

C: 56.71; H: 6.13; N: 13.10

- 10 Found: C: 56.68; H: 6.09; N: 13.12

FAB MS: 414 (MH^+).

EXAMPLE 43

- 15 (*S*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}benzonitrile hydrochloride
-

- Following the procedures described in Example 38, but using (*S*)-3-amino-2-oxo-1-phenethylpyrrolidine hydrochloride (as described in Example 1G) in place of (*R*)-3-amino-1-benzyl-2-oxopyrrolidine hydrochloride in Step C, the above-
- 20 title compound was obtained.

Elemental analysis calculated for $C_{25}H_{27}N_5O \cdot 2 HCl \cdot 0.05 H_2O \cdot 0.15 CHCl_3$:

C: 59.78; H: 5.84; N: 13.86

Found: C: 59.83; H: 5.63; N: 13.75

- 25 FAB MS: 414 (MH^+).

EXAMPLE 44

- 30 (*S*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride
-

Step A: (*S*)-1-(*tert*-Butoxycarbonyl)-3-(trifluoroacetamido)pyrrolidine

- To a stirred solution of (*S*)-3-(trifluoroacetamido)pyrrolidine hydrochloride (2.08 g, 9.5 mmol) and *N,N*-diisopropylethylamine (1.82 mL, 10.5 mmol) in CH_2Cl_2 (25 mL) was added di-*tert*-butyl dicarbonate (2.08 g, 9.5 mmol)
- 35

in CH₂Cl₂ (25 mL). The reaction mixture was stirred at ambient temperature for 2 hrs, then partitioned between saturated aqueous Na₂CO₃ (30 mL) and CH₂Cl₂ (50 mL). The aqueous layer was extracted further with CH₂Cl₂ (50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the titled product.

Step B: (S)-3-Amino-1-(tert-butoxycarbonyl)pyrrolidine

To a stirred solution of (S)-1-(tert-butoxycarbonyl)-3-(trifluoroacetamido)pyrrolidine, as described above in Step A, (2.80 g, 9.5 mmol) in THF (80 mL) and H₂O (10 mL) was added 1.0 N aqueous lithium hydroxide (10.5 mL, 10.5 mmol) and the resulting mixture was stirred at ambient temperature for 18 hrs, then adjusted to pH 7 with 1.0 N aqueous HCl and concentrated to dryness *in vacuo* to give the titled compound.

15 Step C: (S)-3-{[1-(4-Cyanobenzyl)-1H-imidazol-5-ylmethyl]-amino} pyrrolidine-1-carboxylic acid tert-butyl ester

(S)-3-Amino-1-(tert-butoxycarbonyl)pyrrolidine, as described above in from Step B, (1.18 g, 6.34 mmol), 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde, as described in Example 1, Step E, (1.41 g, 6.68 mmol), and acetic acid (0.363 mL, 6.34 mmol) were stirred in MeOH (35 mL) for 30 min then NaCNBH₃ (0.44 g, 7.00 mmol) was added. Stirring was continued for 18 hrs, then the reaction was quenched with 10% aqueous citric acid (5 mL), followed by saturated aqueous Na₂CO₃ (50 mL) and the mixture was extracted with CH₂Cl₂ (2 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ -1% to 7% MeOH - 0.5% NH₄OH, to yield the desired product as a white solid.

Step D: (S)-3-{[1-(4-Cyanobenzyl)-1H-imidazol-5-ylmethyl]-amino} pyrrolidine hydrochloride

30 A solution of (S)-3-{[1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl] amino}pyrrolidine-1-carboxylic acid *tert*-butyl ester, as described above in Step C, (1.92 g, 5.03 mmol) in EtOAc (100 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine hydrochloride as a white solid.

35

Step E: (S)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

- (S)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]-amino} pyrrolidine hydrochloride, as described above in Step D, (40 mg, 0.143 mmol),
 5 1-naphthoic acid (27 mg, 0.157 mmol), EDC (30 mg, 0.157 mmol), 1-hydroxybenzo-triazole hydrate (21 mg, 0.157 mmol), and *N,N*-diisopropylethylamine (27 μ L, 0.157 mmol) were combined in DMF (0.5 mL) and the mixture was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was partitioned between 10% aqueous citric acid (1 mL) and CHCl_3 (2 mL).
 10 The organic layer was discarded, and the aqueous layer was basified by addition of saturated aqueous Na_2CO_3 (1.4 mL) then extracted with CHCl_3 (2×2 mL). The combined organic extracts were dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH_2Cl_2 - 3% MeOH - 0.3% NH_4OH to yield the titled product, which
 15 was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.

Elemental analysis calculated for $\text{C}_{27}\text{H}_{25}\text{N}_5\text{O} \cdot 2.4 \text{ HCl} \cdot 2.3 \text{ H}_2\text{O}$:

C: 57.72; H: 5.72; N: 12.47

Found: C: 57.73; H: 5.72; N: 12.37

- 20 FAB MS: 436 (MH^+).

EXAMPLE 45

- (*R*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 44, but using (*R*)-3-(trifluoroacetamido)pyrrolidine hydrochloride in place of (*S*)-3-(trifluoroacetamido)pyrrolidine hydrochloride in Step A, the above-title compound was obtained.

- 30 Elemental analysis calculated for $\text{C}_{27}\text{H}_{25}\text{N}_5\text{O} \cdot 2.1 \text{ HCl} \cdot 1.1 \text{ H}_2\text{O}$:

C: 61.28; H: 5.55; N: 13.24

Found: C: 61.29; H: 5.54; N: 13.41

FAB MS: 436 (MH^+).

35

EXAMPLE 46

(*S*)-4-(5-{[1-(Naphthalene-2-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

5 Following the procedures described in Example 44, but using 2-naphthoic acid in place of 1-naphthoic acid in Step E, the above-title compound was obtained.

Elemental analysis calculated for $C_{27}H_{25}N_5O \cdot 2 HCl \cdot 1.1 H_2O$:

10 C: 61.70; H: 5.57; N: 13.33

Found: C: 61.69; H: 5.57; N: 13.69

FAB MS: 436 (MH^+).

EXAMPLE 47

15

(*S*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}-benzonitrile trifluoroacetate

 Following the procedures described in Example 44, but using benzoic acid in place of 1-naphthoic acid in Step E, the above-title compound was obtained.

20 The product was purified by semi-preparative HPLC using a Vydac C18 reversed phase column and eluting with a gradient of 95/5 to 0/100 A/B; A = H_2O -0.1% TFA, B = CH_3CN -0.1% TFA.

Elemental analysis calculated for $C_{23}H_{23}N_5O \cdot 2.5 TFA \cdot 1.2 H_2O$:

25 C: 48.65; H: 4.05; N: 10.13

Found: C: 48.68; H: 4.07; N: 9.86

FAB MS: 386 (MH^+).

EXAMPLE 48

30

(*S*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide hydrochloride

Step A: (*S*)-1-Benzoyl-3-(*tert*-butoxycarbonylamino)pyrrolidine

35 To benzoic acid (90 mg, 0.74 mmol) in dry CH_2Cl_2 (3 mL) under

argon were added PYBOP (384 mg, 0.74 mmol), (*S*)-3-(*tert*-butoxycarbonylamino)pyrrolidine (125 mg, 0.67 mmol), and *N,N*-diisopropylethylamine (205 mL, 1.18 mmol). The reaction mixture was stirred for 18 hrs, then quenched with saturated aqueous NaHCO₃ (5 mL) and extracted with CH₂Cl₂ (3 × 3mL). The combined
5 organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane - 50% ethyl acetate to yield the product as a white solid.

Step B: (*S*)-3-Amino-1-benzoylpyrrolidine hydrochloride

10 A solution of (*S*)-1-benzoyl-3-(*tert*-butoxycarbonylamino)pyrrolidine, as described above in Step A, (194 g, 0.67 mmol) in EtOAc (10 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine hydrochloride as a white solid.

15 Step C: (*S*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide hydrochloride

 (*S*)-3-Amino-1-benzoylpyrrolidine hydrochloride, as described above in Step B, (30 mg, 0.16 mmol), lithium [1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetate, as described in Example 16, Step D, (43 mg, 0.17 mmol), EDC (36 mg, 0.19 mmol),
20 1-hydroxybenzotriazole hydrate (26 mg, 0.19 mmol), and *N,N*-diisopropylethylamine (61 µL, 0.35 mmol) were combined in DMF (0.5 mL) and the mixture was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (3 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 3 mL).
25 The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ - 5% MeOH - 0.5% NH₄OH to yield the titled product, which was converted to the hydrochloride salt by treatment with aqueous HCl in acetonitrile.

30 Elemental analysis calculated for C₂₄H₂₃N₅O₂•1.5 HCl•1.1 H₂O:

 C: 59.18; H: 5.50; N: 14.38

Found: C: 59.16; H: 5.51; N: 14.35

FAB MS: 414 (MH⁺).

35

EXAMPLE 49

(*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-[1-(naphthalene-1-carbonyl)-pyrrolidin-3-yl]acetamide hydrochloride

5 Following the procedures described in Example 48, but using 1-naphthoic acid in place of benzoic acid in Step A, the above-titled compound was obtained.

Elemental analysis calculated for C₂₈H₂₅N₅O₂•1.5 HCl:

10 C: 64.89; H: 5.15; N: 13.51

Found: C: 64.87; H: 5.13; N: 13.61

FAB MS: 464 (MH⁺).

EXAMPLE 50

15

(*S*)-4-(5-{[1-(3-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

 Following the procedures described in Example 44, but using 3-chlorobenzoic acid in place of 1-naphthoic acid in Step E, the above-titled compound
20 was obtained.

Elemental analysis calculated for C₂₃H₂₂ClN₅O•2.2 HCl•1.1 H₂O•0.5 CH₃CN:

 C: 53.33; H: 5.20; N: 14.25

Found: C: 53.36; H: 5.08; N: 14.25

25 FAB MS: 420 (MH⁺).

EXAMPLE 51

(*R*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}-benzonitrile
30 hydrochloride

 Following the procedures described in Example 44, but using (*R*)-3-(trifluoroacetamido)pyrrolidine hydrochloride in place of (*S*)-3-(trifluoroacetamido)pyrrolidine hydrochloride in Step A, and benzoic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

35

Elemental analysis calculated for $C_{23}H_{23}N_5O \cdot 2.1 HCl \cdot 0.9 H_2O$:

C: 57.98; H: 5.68; N: 14.70

Found: C: 57.95; H: 5.67; N: 14.78

FAB MS: 386 (MH^+).

5

EXAMPLE 52

(*S*)-4-(5- {[1-(2-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

10 Following the procedures described in Example 44, but using 2-chlorobenzoic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{23}H_{22}ClN_5O \cdot 3 HCl \cdot 0.65 H_2O \cdot 0.2 Et_2O$:

15 C: 54.93; H: 5.48; N: 13.46

Found: C: 54.90; H: 5.31; N: 13.42

FAB MS: 420 (MH^+).

EXAMPLE 53

20

(*S*)-4-(5- {[1-(2-Methylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

25 Following the procedures described in Example 44, but using 2-methylnicotinic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{23}H_{24}N_6O \cdot 3 HCl \cdot 0.45 H_2O \cdot 0.6 THF$:

C: 54.35; H: 5.87; N: 14.98

Found: C: 54.40; H: 5.84; N: 14.94

30 FAB MS: 401 (MH^+).

EXAMPLE 54

35 (*S*)-4-(5- {[1-(Isoquinoline-4-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 44, but using 4-isoquinolinecarboxylic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

5 Elemental analysis calculated for $C_{26}H_{24}N_6O \cdot 2.5 HCl \cdot 1.6 H_2O$:

C: 56.20; H: 5.40; N: 15.13

Found: C: 56.17; H: 5.40; N: 14.93

FAB MS: 437 (MH^+).

10

EXAMPLE 55

(*S*)-4-(5-{[1-(5-Bromopyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

15 Following the procedures described in Example 44, but using 5-bromonicotinic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{22}H_{21}BrN_6O \cdot 3 HCl \cdot 0.9 H_2O \cdot 0.5 PhCH_3$:

C: 48.08; H: 4.72; N: 13.19

20 Found: C: 48.09; H: 4.48; N: 13.18

FAB MS: 465 (MH^+).

EXAMPLE 56

25 (*S*)-4-(5-{[1-(2-Methylthiopyridine-3-carbonyl)pyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 44, but using 2-(methylthio)nicotinic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

30

Elemental analysis calculated for $C_{23}H_{24}N_6OS \cdot 3 HCl \cdot 0.45 H_2O \cdot 0.35 PhCH_3$:

C: 52.49; H: 5.31; N: 14.43

Found: C: 52.51; H: 5.15; N: 14.33

FAB MS: 433 (MH^+).

35

EXAMPLE 57

4-(5-{[(3*S*)-1-(2-Ethylthiopyridine-3-carbonyl)pyrrolidin-3-ylamino]-methyl}
imidazol-1-ylmethyl)benzonitrile hydrochloride

- 5 Following the procedures described in Example 44, but using 2-(ethylthio)nicotinic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

Elemental analysis calculated for $C_{24}H_{26}N_6OS \cdot 2.4 HCl \cdot 1.9 H_2O$:

10 C: 50.80; H: 5.70; N: 14.81

Found: C: 50.82; H: 5.71; N: 14.88

FAB MS: 447 (MH^+).

EXAMPLE 58

15

4-(5-{[(3*S*)-1-(*trans*-Cotinine-4-carbonyl)pyrrolidin-3-ylamino]methyl}-imidazol-1-ylmethyl)benzonitrile hydrochloride

- Following the procedures described in Example 44, but using *trans*-4-cotininecarboxylic acid in place of 1-naphthoic acid in Step E, the above-titled
20 compound was obtained.

Elemental analysis calculated for $C_{27}H_{29}N_7O_2 \cdot 2.5 HCl \cdot 1.6 H_2O \cdot 0.5 CH_3CN$:

C: 54.75; H: 5.88; N: 16.51

Found: C: 54.77; H: 6.15; N: 16.51

25 FAB MS: 484 (MH^+).

EXAMPLE 59

(*S*)-4-(5-{[1-(Biphenyl-2-carbonyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

- 30 Following the procedures described in Example 44, but using biphenyl-2-carboxylic acid in place of 1-naphthoic acid in Step E, the above-titled compound was obtained.

35 Elemental analysis calculated for $C_{29}H_{27}N_5O \cdot HCl \cdot 2.1 H_2O$:

C: 63.11; H: 5.88; N: 12.69

Found: C: 63.12; H: 5.88; N: 12.92

FAB MS: 462 (MH^+).

5

EXAMPLE 60

(S)-4-(5-{[1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino]methyl}-
imidazol-1-ylmethyl)benzonitrile hydrochloride

10 Following the procedures described in Example 44, but using 1-
adamantylacetic acid in place of 1-naphthoic acid in Step E, the above-titled
compound was obtained.

Elemental analysis calculated for $\text{C}_{28}\text{H}_{35}\text{N}_5\text{O} \cdot 2 \text{HCl} \cdot 0.9 \text{H}_2\text{O} \cdot 0.2 \text{EtOAc}$:

C: 61.29; H: 7.22; N: 12.41

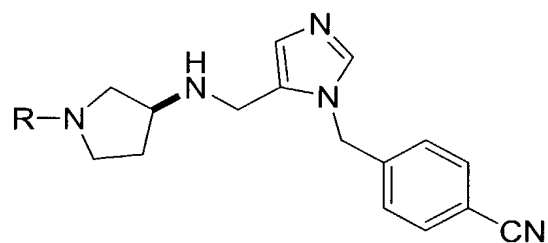
15 Found: C: 61.34; H: 7.16; N: 12.39

FAB MS: 458 (MH^+).

EXAMPLES 61-126

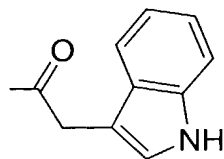
20 Table 1: Examples 61 -126

Following the procedures described in Example 44, but using the
appropriate carboxylic acid in place of 1-naphthoic acid in Step E, the following
compound were obtained. The crude products from corresponding Step E were not
purified on silica gel.



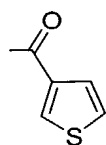
| <u>EXAMPLE</u> | <u>R</u> | <u>FAB MS (MH⁺)</u> |
|----------------|----------|--------------------------------|
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| 62 | | 376 |
| 63 | | 392 |
| 64 | | 425 |
| 65 | | 425 |

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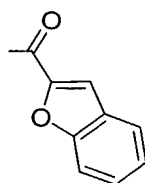
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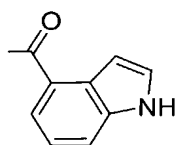
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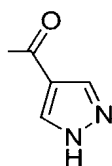
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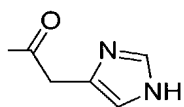
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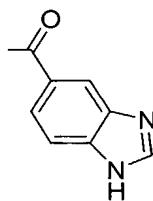
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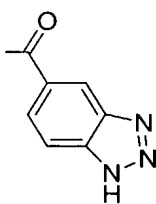
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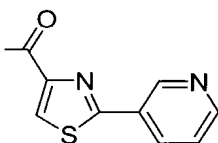
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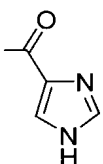
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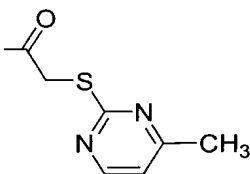
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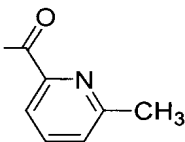
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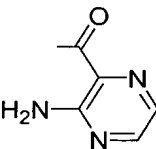
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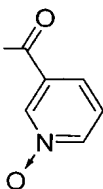
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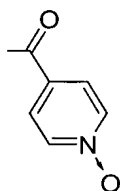
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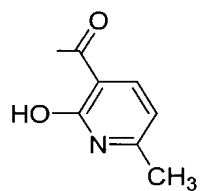
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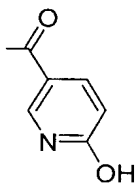
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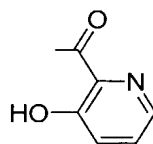
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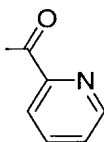
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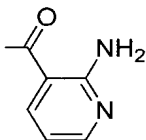
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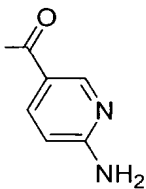
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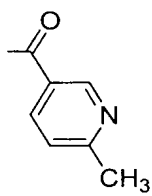
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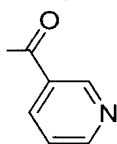
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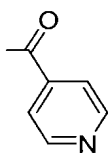
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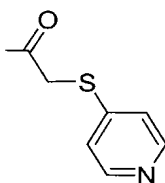
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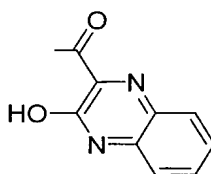
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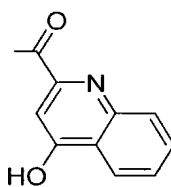
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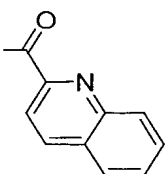
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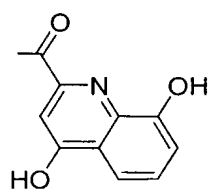
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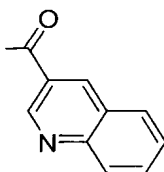
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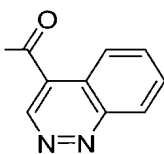
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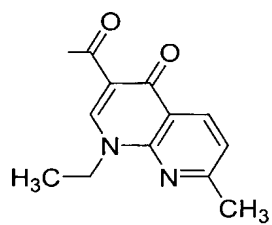
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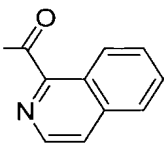
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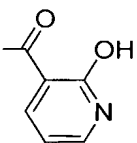
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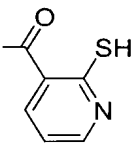
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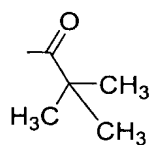
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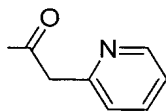
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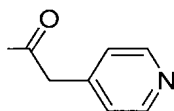
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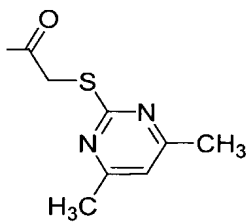
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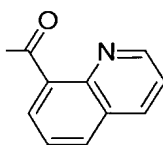
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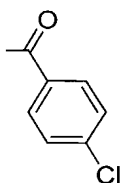
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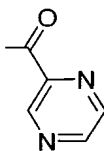
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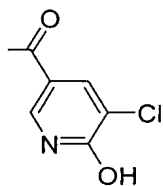
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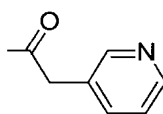
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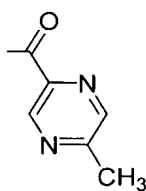
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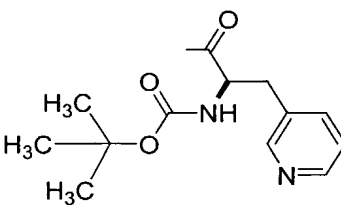
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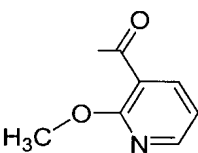
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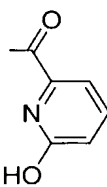
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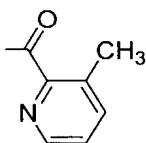
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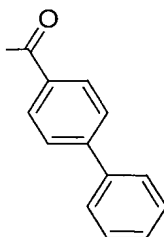
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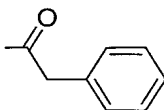
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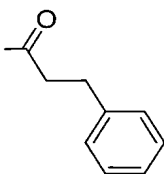
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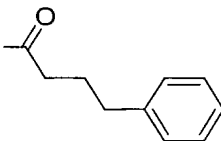
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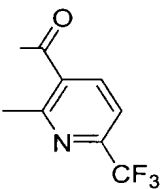
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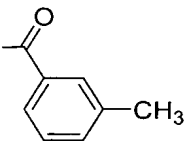
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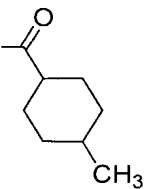
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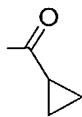
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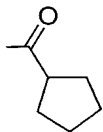
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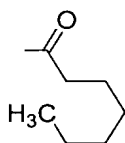
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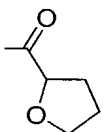
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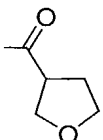
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126



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EXAMPLE 127

5 (S)-4-(5- {[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenoxybenzonitrile hydrochloride

Step A: 4-(Hydroxymethyl)-1-(triphenylmethyl)imidazole

10 To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in dry DMF (250 mL) at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in DMF (500 mL) was added dropwise. The reaction mixture was stirred for 20 hrs, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to

15 provide the titled product as a white solid.

Step B: 4-(Acetoxymethyl)-1-(triphenylmethyl)imidazole

4-(Hydroxymethyl)-1-(triphenylmethyl)imidazole, as described above in Step A, (88.5 g, 260 mmol) was suspended in pyridine (500 mL). Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hrs during which it became homogeneous. The solution was poured into EtOAc, washed sequentially with water, 5% aqueous HCl solution, saturated aqueous NaHCO₃ solution, and brine. The organic extracts were dried (Na₂SO₄), and concentrated *in vacuo* to provide the ester as a white powder.

Step C: 4-Cyano-3-fluorotoluene

To a deoxygenated solution of 4-bromo-3-fluorotoluene (25.0 g, 132 mmol) in DMF (500 mL) was added Zn(CN)₂ (10.1 g, 86 mmol) and Pd(PPh₃)₄ (15 g, 13 mmol). The reaction was stirred at 100°C for 18 hrs, then cooled to room temperature. The solution was poured into toluene (1 L), washed with 30% aqueous NH₄OH (2 × 1 L), then brine (800 mL), then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography, eluting with a gradient of hexane -0% to 7% EtOAc, to yield the titled product.

Step D: 4-Cyano-3-fluorobenzylbromide

To a solution of 4-cyano-3-fluorotoluene, as described above in Step C, (5.0 g, 37.0 mmol) in carbon tetrachloride (300 mL) was added *N*-bromosuccinimide (7.57 g, 42.6 mmol) and 2,2'-azobisisobutyronitrile (610 mg, 3.7 mmol). The reaction mixture was heated to reflux under argon for 24 hrs, then cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of hexane -4% to 7% EtOAc, to yield the titled product as a yellow solid.

Step E: 5-(Acetoxymethyl)-1-(4-cyano-3-fluorobenzyl)imidazole hydrobromide

A mixture of 4-(acetoxymethyl)-1-(triphenylmethyl) imidazole, as describe aboved in Step B, (19.7 g, 51.4 mmol) and 4-cyano-3-fluorobenzylbromide, as described above in Step D, (11.0 g, 51.4 mmol) in dry CH₃CN (140 mL) was stirred at 50°C for 3 hrs, during which a white precipitate formed. The reaction was

cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume of 70 mL, reheated at 50°C for 2 hrs, cooled to room temperature, and filtered again. The solid material was combined and dissolved in MeOH (500 mL), and the solution was heated to reflux
5 for 2 hrs. The solution was concentrated *in vacuo* to a volume of 20 mL, then cold hexane - EtOAc (1:1, 500 mL) was added and the white precipitate was collected and dried *in vacuo* to obtain the titled compound.

Step F: 1-(4-Cyano-3-fluorobenzyl)-5-(hydroxymethyl)imidazole
10 To a solution of 5-(acetoxymethyl)-1-(4-cyano-3-fluorobenzyl) imidazole hydrobromide, as described above in Step E, (19.8 g, 72.5 mmol) in 5:1 THF/water (430 mL) at ambient temperature was added lithium hydroxide monohydrate (3.33 g, 79.4 mmol). After 4 hrs, the solution was adjusted to pH 7 with 1.0 N hydrochloric acid and concentrated *in vacuo*. The residue was
15 concentrated from toluene *in vacuo* (3 × 100 mL) to give the titled product as a pale solid.

Step G: 1-(4-Cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde
20 To a solution of 1-(4-cyano-3-fluorobenzyl)-5-(hydroxymethyl) imidazole, as described above in Step F, (2.31 g, 10.0 mmol) in DMSO (20 mL) at 0°C was added triethylamine (5.6 mL, 40 mmol), then SO₃-pyridine complex (3.89 g, 25 mmol). After 30 minutes, the reaction was poured into EtOAc (400 mL), washed with water (4 × 50 mL), then brine (50 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the aldehyde as a pale yellow powder.

25
Step H: (S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile
 (S)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride
 (as described in Example 1I) (74 mg, 0.28 mmol) and 1-(4-cyano-3-fluorobenzyl)-
30 5-imidazolecarboxaldehyde, as described above in Step G, (68 mg, 0.30 mmol), were stirred in MeOH (1 mL) and *N,N*-diisopropylethylamine was added dropwise to adjust the mixture to ca. pH 5, as judged by wetted pH paper. The mixture was stirred for 1 hr at ambient temperature then NaCNBH₃ (21 mg, 0.33 mmol) was added, AcOH was added to adjust the mixture to about pH 5, and stirring was continued for 18 hrs. The
35 reaction mixture was concentrated under reduced pressure, and the residual solution

was partitioned between saturated aqueous NaHCO₃ (1 mL) and CH₂Cl₂ (3 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 3 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a
 5 gradient of CH₂Cl₂ - 0% to 5% MeOH - 0% to 0.5% NH₄OH to yield the titled product as a colorless oil.

Step I: (S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)-2-phenoxybenzonitrile hydrochloride

10 A mixture of (S)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile, as described above in Step H, (29 mg, 0.066 mmol), phenol (7.5 mg, 0.079 mmol) and Cs₂CO₃ (42 mg, 0.129 mmol) in dry, degassed DMF (1 mL) was stirred at 40°C under argon for 6
 15 hrs. The reaction mixture was partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted further with CH₂Cl₂ (10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CHCl₃ - 0% to 3% MeOH - 0% to 0.3% NH₄OH to yield
 20 the titled product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

Elemental analysis calculated for C₂₉H₂₆ClN₅O₂•2 HCl•0.4 H₂O•0.15 EtOAc:

C: 58.72; H: 5.00; N: 11.57

Found: C: 58.70; H: 4.82; N: 11.54

25 FAB MS: 512 (MH⁺).

EXAMPLE 128

30 (S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile hydrochloride

To a suspension of potassium *tert*-butoxide (98 mg, 0.87 mmol) in dry THF (10 mL), under argon, at 0°C was added phenethyl alcohol (106 mg, 0.87 mmol). The mixture was stirred for 30 min at 0°C, then a 1 mL aliquot was added dropwise to a solution of (S)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile, as described in Example
 35

127, Step H, (38 mg, 0.087 mmol) in dry THF (2 mL) at -78°C . The reaction mixture was stirred at -78°C for 2 hrs, then partitioned between saturated aqueous NaHCO_3 (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted further with CH_2Cl_2 (10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CHCl_3 - 1% to 3% MeOH - 0.1% to 0.3% NH_4OH to yield the titled product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

10 Elemental analysis calculated for $\text{C}_{31}\text{H}_{30}\text{ClN}_5\text{O}_2 \cdot 2 \text{HCl} \cdot 1.1 \text{H}_2\text{O}$:

C: 58.83; H: 5.45; N: 11.07

Found: C: 58.83; H: 5.07; N: 11.02

FAB MS: 540 (MH^+).

15 EXAMPLE 129

(R)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenoxybenzonitrile hydrochloride

20 Following the procedures described in Example 127, but using (R)-3-amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride (as described in Example 1H) in place of (S)-3-amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride in Step H, the above-titled compound was obtained.

Elemental analysis calculated for $\text{C}_{29}\text{H}_{26}\text{ClN}_5\text{O}_2 \cdot 2 \text{HCl} \cdot 0.75 \text{H}_2\text{O} \cdot 0.2 \text{EtOAc}$:

25 C: 58.09; H: 5.09; N: 11.37

Found: C: 58.11; H: 5.14; N: 11.36

FAB MS: 512 (MH^+).

30 EXAMPLE 130

(R)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile hydrochloride

35 Following the procedures described in Example 128, but using (R)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile [prepared as described in Example 127, Steps A-H, but using (R)-

3-amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride (as described in Example 1H) instead of (*S*)-3-amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride in Step H] in place of (*S*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile, the above-titled compound was obtained.

5

Elemental analysis calculated for $C_{31}H_{30}ClN_5O_2 \cdot 2 HCl \cdot 0.1 H_2O \cdot 0.3 CH_2Cl_2$:

C: 58.71; H: 5.16; N: 10.94

Found: C: 58.66; H: 4.88; N: 11.12

FAB MS: 540 (MH^+).

10

EXAMPLE 131

(*S*)-2-Benzyloxy-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

15

Following the procedures described in Example 128, but using benzyl alcohol in place of phenethyl alcohol, the above-titled compound was obtained.

Elemental analysis calculated for $C_{30}H_{28}ClN_5O_2 \cdot 2 HCl \cdot 0.25 CH_2Cl_2 \cdot 0.1 EtOAc$:

C: 58.52; H: 5.02; N: 11.13

20

Found: C: 58.47; H: 5.00; N: 11.11

FAB MS: 526 (MH^+).

EXAMPLE 132

(*R*)-2-Benzyloxy-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Following the procedures described in Example 128, but using benzyl alcohol in place of phenethyl alcohol, and (*R*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile [prepared as described in Example 127, Steps A-H, but using (*R*)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride (as described in Example 1H) instead of (*S*)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride in Step H] in place of (*S*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile, the above-titled compound was obtained.

35

Elemental analysis calculated for $C_{30}H_{28}ClN_5O_2 \cdot 2 HCl \cdot 0.2 CH_2Cl_2 \cdot 0.05 EtOAc$:

C: 58.85; H: 5.00; N: 11.29

Found: C: 58.82; H: 5.02; N: 11.28

FAB MS: 526 (MH^+).

5

EXAMPLE 133

(*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile hydrochloride

10 Following the procedures described in Example 128, but using 3-phenylpropanol in place of phenethyl alcohol, the above-titled compound was obtained.

Elemental analysis calculated for $C_{32}H_{32}ClN_5O_2 \cdot 2 HCl \cdot 0.15 CH_2Cl_2 \cdot 0.05 H_2O$:

15 C: 60.27; H: 5.41; N: 10.93

Found: C: 60.24; H: 5.16; N: 10.89

FAB MS: 554 (MH^+).

EXAMPLE 134

20

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile hydrochloride

25 Following the procedures described in Example 128, but using 3-phenylpropanol in place of phenethyl alcohol, and (*R*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile [prepared as described in Example 127, Steps A-H, but using (*R*)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride (as described in Example 1H) instead of (*S*)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride in Step H] in place of (*S*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile in Step A, the above-titled compound was obtained.

30

Elemental analysis calculated for $C_{32}H_{32}ClN_5O_2 \cdot 2 HCl \cdot 0.1 CH_2Cl_2 \cdot 0.1 H_2O$:

C: 60.49; H: 5.44; N: 10.99

Found: C: 60.51; H: 5.19; N: 10.84

35 FAB MS: 554 (MH^+).

EXAMPLE 135

5 (S)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl}imidazol-
1-ylmethyl)-2-methoxybenzonitrile hydrochloride

Step A: Methyl 4-amino-3-hydroxybenzoate

10 Through a solution of 4-amino-3-hydroxybenzoic acid (75 g, 0.49 mol) in dry methanol (2 L) at ambient temperature was bubbled anhydrous HCl gas until the solution was saturated. The solution was stirred for 48 hours, then concentrated *in vacuo*. The product was partitioned between EtOAc and saturated aqueous NaHCO₃ solution, and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated *in vacuo* to provide the title compound.

15 Step B: Methyl 3-hydroxy-4-iodobenzoate

A cloudy, dark solution of methyl 4-amino-3-hydroxybenzoate from Step A (79 g, 0.47 mol) in 3N HCl (750 mL), and THF (250 mL) was cooled to 0°C. A solution of NaNO₂ (35.9 g, 0.52 mol) in 115 mL of water was added over ca. 5 minutes, and the solution was stirred for another 25 minutes. A solution of
20 potassium iodide (312 g, 1.88 mol) in 235 mL of water was added all at once, and the reaction was stirred for an additional 15 minutes. The mixture was poured into EtOAc, shaken, and the layers were separated. The organic phase was washed with water and brine, dried (Na₂SO₄), and concentrated *in vacuo* to provide the crude product (148 g). The crude product was purified by flash column chromatography
25 on silica, eluting with a gradient of hexane - 20% to 50% EtOAc to yield the title product.

Step C: Methyl 4-cyano-3-hydroxybenzoate

30 A mixture of methyl 3-hydroxy-4-iodobenzoate, as described above in Step B, (101 g, 0.36 mol) and zinc(II)cyanide (30 g, 0.25 mol) in dry DMF (400 mL) was degassed by bubbling argon through the solution for 20 minutes. Tetrakis (triphenylphosphine)palladium (8.5 g, 7.2 mmol) was added, and the solution was heated to 80°C for 4 hours. The solution was cooled to ambient temperature, then stirred for an additional 36 hours. The reaction was poured into EtOAc (3 L) and

water (1 L) and the organic layer was washed with brine (4 × 500 mL), dried (Na₂SO₄), and concentrated *in vacuo* to provide the crude product. The crude product was partially purified by flash column chromatography on silica, eluting with a gradient of hexane - 25% to 50% EtOAc, then crystallized from EtOAc-hexane to yield the title product.

Step D: Methyl 4-cyano-3-methoxybenzoate

Sodium hydride (13.9 g of a 60 wt. % dispersion in mineral oil, 0.348 mol) was added to a solution of methyl 4-cyano-3-hydroxybenzoate, as described above in Step C, (56 g, 0.316 mol) in dry DMF (600 mL) at 0°C, and the mixture was stirred for 20 min at ambient temperature. Iodomethane (49.4 g, 0.348 mol) was added, and the reaction mixture was stirred for 2 hours, then partitioned between EtOAc (2 L) and water (1 L). The aqueous layer was extracted further with EtOAc (1 L). The combined organic extracts were washed with saturated aqueous Na₂CO₃ (1 L), then water (1 L), then brine (2 × 1 L), then dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide the title product.

Step E: 4-Cyano-3-methoxybenzyl alcohol

To a solution of methyl 4-cyano-3-methoxybenzoate, as described above in Step D, (59.1 g, 0.309 mol) in dry THF (600 mL), under argon, at ambient temperature was added lithium borohydride (309 mL of a 2 M solution in THF, 0.618 mol) over 10 min. After 3 hrs, the reaction mixture was warmed to reflux for 45 min, then cooled to room temperature. The solution was poured into EtOAc (1 L) and 1 N aqueous HCl (1 L) [CAUTION], and the layers were separated. The organic layer was washed with water (500 mL), saturated aqueous Na₂CO₃ (500 mL), and brine (2 × 500 mL), dried (Na₂SO₄), and concentrated *in vacuo* to provide the title product.

Step F: 4-Cyano-3-methoxybenzyl bromide

A solution of 4-cyano-3-methoxybenzyl alcohol, as described above in Step E, (40.3 g, 0.247 mol) in dry THF (600 mL) was cooled to 0°C. Triphenylphosphine (97.2 g, 0.370 mol) was added, followed by carbon tetrabromide (122.9 g, 0.370 mol). The reaction mixture was stirred at 0°C for 15 min, then at ambient temperature for 30 min, then concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ (2 L) and saturated aqueous NaHCO₃ (1 L). The organic layer

was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of hexane - 25% to 35% EtOAc to yield the title product.

- 5 Step G: (S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile hydrochloride
 Following the procedures described in Example 1, but using 4-cyano-3-methoxybenzyl bromide (as described above in Step F) in place of 4-cyanobenzyl bromide in Step C, 3-chlorobenzylamine in place of aniline in Step F, and (S)-N-(*tert*-
 10 butoxycarbonyl)methionine in place of (R)-N-(*tert*-butoxycarbonyl)methionine in Step F, the above-titled compound was obtained.

Elemental analysis calculated for C₂₄H₂₄ClN₅O₂•2 HCl•0.25 CH₂Cl₂•0.55 EtOAc:

C: 53.61; H: 5.26; N: 11.82

- 15 Found: C: 53.61; H: 5.00; N: 11.81

FAB MS: 450 (MH⁺).

EXAMPLE 136

- 20 (R)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile hydrochloride

- Following the procedures described in Example 1, but using 4-cyano-3-methoxybenzyl bromide (as described in Example 135, Step F) in place of 4-cyanobenzyl bromide in Step C, and 3-chlorobenzylamine in place of aniline
 25 in Step F, the above-titled compound was obtained.

Elemental analysis calculated for C₂₄H₂₄ClN₅O₂•2 HCl•0.55 CH₂Cl₂•0.15 C₆H₅CH₃:

C: 54.19; H: 5.03; N: 12.34

Found: C: 54.26; H: 5.00; N: 12.35

- 30 FAB MS: 450 (MH⁺).

EXAMPLE 137

- 35 (S)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

Step A: (S)-N-(tert-Butoxycarbonyl)homoserine lactone

(S)-N-(tert-Butoxycarbonyl)homoserine (2.00 g, 9.12 mmol), EDC (1.92 g, 10.04 mmol), 1-hydroxybenzotriazole hydrate (1.36 g, 10.04 mmol), and
5 N,N-diisopropylethylamine (103 mL, 0.59 mmol) were combined in DMF (20 mL) and the mixture was stirred at ambient temperature for 3 hrs. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous NaHCO₃ (30 mL) and EtOAc (50 mL). The aqueous layer was extracted further with CH₂Cl₂ (50 mL). The combined organic extracts were dried over
10 Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane - 50% EtOAc, to yield the titled product as a white solid.

Step B: (S)-2-(tert-Butoxycarbonylamino)-4-hydroxy-N-pyridin-2-ylbutyramide

To a stirred solution of 2-aminopyridine (257 mg, 2.73 mmol) in dry CH₂Cl₂ (7 mL) at ambient temperature, under argon, was added trimethylaluminum (1.37 mL of a 2.0 N solution in hexane, 2.73 mmol) dropwise. The resulting mixture was stirred for 15 min, then (S)-N-(tert-butoxycarbonyl)homoserine lactone, as
20 described above in Step A, (500 mg, 2.48 mmol) in CH₂Cl₂ (5 mL) was added and stirring was continued at ambient temperature for 18 hrs. The reaction was quenched carefully with 10% aqueous citric acid (5 mL) and, after effervescence had stopped, the mixture was partitioned between saturated aqueous potassium sodium tartrate (30 mL) and CH₂Cl₂ (30 mL). The aqueous layer was extracted further with CH₂Cl₂
25 (2 × 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of EtOAc - 20% to 5% hexane to yield the titled product.

Step C: (S)-3-(tert-Butoxycarbonylamino)-2-oxo-1-pyridin-2-ylpyrrolidine hydrochloride

Tri-*n*-butylphosphine (0.172 mL, 0.69 mmol) and di-*tert*-butyl azodicarboxylate (159 mg, 0.69 mmol) were combined in dry THF (1 mL) at ambient temperature and stirred for 5 min, then added dropwise to a solution of (S)-2-(tert-butoxycarbonylamino)-4-hydroxy-N-pyridin-2-ylbutyramide, as described above in
35

Step B, (102 mg, 0.345 mmol) in THF (0.5 mL) at 0°C, under argon. The resulting mixture was allowed to warm slowly to ambient temperature and stirred for 18 hrs, then partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted further with CH₂Cl₂ (10 mL). The combined
5 organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of hexane - 30% to 40% EtOAc to yield the titled product.

Step D: (S)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-
10 1-ylmethyl}benzonitrile hydrochloride

Following the procedures described in Example 1, but using (S)-3-(*tert*-butoxycarbonylamino)-2-oxo-1-pyridin-2-ylpyrrolidine hydrochloride (as described above in Step C) in place of (R)-3-(*tert*-butoxycarbonylamino)-2-oxo-1-phenylpyrrolidine hydrochloride in Step I, the above-titled compound was obtained.

Elemental analysis calculated for C₂₁H₂₀N₆O•2.5 HCl•0.4 H₂O•0.1 EtOAc:

C: 53.59; H: 5.07; N: 17.52

Found: C: 53.53; H: 5.17; N: 17.53

FAB MS: 373 (MH⁺).

EXAMPLE 138

(S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](3-phenylpropyl)amino} methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

Following the procedures described in Example 24, but using 3-phenylpropionaldehyde in place of benzaldehyde and (S)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride (as described in Example 12) in place of (S)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile in Step A, the above-titled
30 compound was obtained.

Elemental analysis calculated for C₃₂H₃₂ClN₅O•2 HCl•0.1 EtOAc:

C: 62.78; H: 5.66; N: 11.30

Found: C: 62.94; H: 5.85; N: 11.25

FAB MS: 538 (MH⁺).

EXAMPLE 139

(*S*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino} methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

Following the procedures described in Example 35, but using (*S*)-4-(5-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl}imidazol-1-ylmethyl) benzonitrile hydrochloride (as described in Example 12) in place of (*S*)-4-{5-[(1-benzyl-2-oxopyrrolidin-3-ylamino) methyl]imidazol-1-ylmethyl} benzonitrile in Step B, the above-titled compound was obtained.

Elemental analysis calculated for $C_{26}H_{29}ClN_6O \cdot 3 HCl \cdot 0.15 H_2O$:

C: 53.01; H: 5.53; N: 14.27

Found: C: 52.96; H: 5.71; N: 14.34

FAB MS: 477 (MH^+).

EXAMPLE 140

(*S*)-*N*-(3-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide hydrochloride

To a stirred mixture of (*S*)-4-[5-({(3-aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl] benzonitrile hydrochloride (as described in Example 139) (20 mg, 0.034 mmol) and nicotinoyl chloride hydrochloride (7 mg, 0.039 mmol) in CH_2Cl_2 (0.5 mL) was added *N,N*-diisopropylethylamine (35 mL, 0.20 mmol) and stirring was continued at ambient temperature for 5 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted further with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH_2Cl_2 - 1% to 5% MeOH - 0.1% to 0.5% NH_4OH to yield the titled product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

Elemental analysis calculated for $C_{32}H_{32}ClN_7O_2 \cdot 3 HCl \cdot 1.35 H_2O \cdot 0.45 EtOAc$:

C: 53.74; H: 5.51; N: 12.98

Found: C: 53.74; H: 5.58; N: 13.01
FAB MS: 582 (MH⁺).

EXAMPLE 141

5

(S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

Step A: 2-(tert-Butyldimethylsilyloxy)ethanol

10

To a stirred suspension of NaH (0.64 g of a 60 wt. % dispersion in mineral oil, 16 mmol) in dry THF, under argon, was added ethylene glycol (1.00 g, 16 mmol) and the resulting mixture was allowed to stir for 45 min at ambient temperature. *tert*-Butyldimethylsilyl chloride (2.43 g, 16 mmol) was added in one portion, and stirring was continued for 45 min. The reaction mixture was poured into Et₂O (200 mL) and washed with saturated aqueous Na₂CO₃ (100 mL) and then brine (100 mL), then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane - 30% EtOAc to yield the titled product as a colorless oil.

15

20

Step B: 2-(tert-Butyldimethylsilyloxy)ethanal

25

To a stirred solution of oxalyl chloride (1.43 mL, 16.4 mmol) in dry CH₂Cl₂ (20 mL) at -70°C, under argon, was added dry DMSO (2.33 mL, 32.8 mmol) dropwise, over 5 min. The resulting mixture was stirred at -70°C for 30 min, then a solution of 2-(*tert*-butyldimethylsilyloxy)ethanol, as described above in Step A, (2.23 g, 12.6 mmol) in CH₂Cl₂ (10 mL) was added slowly. After stirring for an additional 15 min, triethylamine (8.8 mL, 63 mmol) was added and the mixture was allowed to warm to -40°C, then partitioned between CH₂Cl₂ (100 mL) and saturated aqueous NaHCO₃ (50 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with CH₂Cl₂ to yield the desired aldehyde.

30

Step C: (S)-4-[5-({[2-(*tert*-Butyldimethylsilyloxy)ethyl][1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile

35

(S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]-methyl})

imidazol-1-ylmethyl)benzonitrile hydrochloride (as described in Example 12) (203 mg, 0.48 mmol), 2-(*tert*-butyldimethylsilyloxy)ethanal, as described above in Step B, (126 mg, 0.72 mmol), and acetic acid (58 mg, 0.96 mmol) were stirred in MeOH (2 mL) for 30 min then NaCNBH₃ (60 mg, 0.96 mmol) was added. Stirring was continued for 18 hrs, then most of the MeOH was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (20 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 1% to 3% MeOH - 0.1% to 0.3% NH₄OH, to yield the desired product.

Step D: (S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-hydroxyethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile

To a solution of (S)-4-[5-({[2-(*tert*-butyldimethylsilyloxy)ethyl] [1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile, as described above in Step C, (175 mg, 0.303 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (0.363 mL of a 1.0 M solution in THF, 0.363 mmol). The reaction mixture was stirred for 1 hr, then poured into H₂O (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a gradient of CH₂Cl₂ - 1% to 6% MeOH - 0.1% to 0.6% NH₄OH, to yield the desired product as a colorless oil.

Step E: (S)-2-{{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}acetaldehyde

To a stirred solution of oxalyl chloride (35 mL, 0.39 mmol) in dry CH₂Cl₂ (2 mL) at -70°C, under argon, was added dry DMSO (56 mL, 0.78 mmol) dropwise, over 2 min. The resulting mixture was stirred at -70°C for 10 min, then a solution of (S)-4-[5-({[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl](2-hydroxyethyl)amino}methyl)imidazol-1-ylmethyl]-benzonitrile, as described above in Step D, (140 mg, 0.30 mmol) in CH₂Cl₂ (3 mL) was added slowly. After stirring for an additional 15 min, triethylamine (0.21 mL, 1.51 mmol) was added and the mixture was allowed to warm to ambient temperature, then partitioned between CH₂Cl₂ (20 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted further

with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield the desired aldehyde.

Step F: (S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino} methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

(S)-2-{{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}acetaldehyde, as described above in Step E (46 mg, 0.10 mmol), morpholine (10 mL, 0.11 mmol), and acetic acid (40 mL, 0.70 mmol) were stirred in MeOH (2 mL) for 30 min then NaCNBH₃ (13 mg, 0.21 mmol) was added. Stirring was continued for 18 hrs, then most of the MeOH was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (20 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was partially purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 1% to 5% MeOH - 0.1% to 0.5% NH₄OH, then further purified by semi-preparative HPLC using a Vydac C18 reversed phase column and eluting with a gradient of 95/5 to 0/100 A/B; A = H₂O-0.1% TFA, B = CH₃CN-0.1% TFA. The pure fractions were collected and extracted from saturated aqueous Na₂CO₃ (2 mL) with CHCl₃ (15 mL), and the CHCl₃ layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the titled product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

Elemental analysis calculated for C₂₉H₃₃ClN₆O₂•3 HCl•0.3 EtOAc•0.1 CH₂Cl₂:

C: 53.72; H: 5.74; N: 12.41

Found: C: 53.72; H: 6.09; N: 12.40

FAB MS: 533 (MH⁺).

EXAMPLE 142

(S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino} methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

Step A: (S)-4-[5-({[2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)ethyl][1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile

5 (S)-2-{{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}acetaldehyde (as described in Example 141, Step E) (46 mg, 0.10 mmol), 1-*tert*-butoxycarbonylpiperazine (22 mg, 0.12 mmol), and acetic acid (40 mL, 0.70 mmol) were stirred in MeOH (2 mL) for 30 min then NaCNBH₃ (13 mg, 0.21 mmol) was added. Stirring was continued for 18 hrs, then most of the
10 MeOH was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (5 mL) and CH₂Cl₂ (20 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by semi-preparative HPLC using a Vydac C18 reversed phase column and eluting with
15 a gradient of 95/5 to 0/100 A/B; A = H₂O-0.1% TFA, B = CH₃CN-0.1% TFA. The pure fractions were collected and extracted from saturated aqueous NaHCO₃ (2 mL) with CH₂Cl₂ (100 mL), and the CH₂Cl₂ layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the desired product.

20 Step B: (S)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride

A solution of (S)-4-[5-({[2-(4-*tert*-butoxycarbonylpiperazin-1-yl)ethyl][1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile, as described above in Step A, (20 mg, 0.032 mmol) in EtOAc (5 mL)
25 at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo*, and the residue was purified by semi-preparative HPLC using a Vydac C18 reversed phase column and eluting with a gradient of 95/5 to 0/100 A/B; A = H₂O-0.1% TFA, B = CH₃CN-0.1% TFA. The pure fractions were collected and extracted from saturated aqueous NaHCO₃ (2 mL) with CH₂Cl₂ (15 mL), and the CH₂Cl₂ layer
30 was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the desired product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

35

Elemental analysis calculated for $C_{29}H_{34}ClN_7O \cdot 4 HCl \cdot 2.25 H_2O \cdot 0.2 CH_2Cl_2$:

C: 50.10; H: 6.18; N: 14.01

Found: C: 50.13; H: 6.18; N: 13.92

FAB MS: 532 (MH^+).

5

EXAMPLE 143

(S)-4-[5-([1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][2-(pyridin-2-ylamino)ethylamino)methyl]imidazol-1-ylmethyl]benzonitrile hydrochloride

10 Following the procedures described in Example 141, but using 2-aminopyridine in place of morpholine in Step F, the above-titled compound was obtained.

Elemental analysis calculated for $C_{30}H_{30}ClN_7O \cdot 3 HCl \cdot 0.3 EtOAc$:

15 C: 55.44; H: 5.28; N: 14.51

Found: C: 55.70; H: 5.65; N: 14.50

FAB MS: 540 (MH^+).

EXAMPLE 144

20

(S)-6-Amino-N-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1H-imidazol-5-ylmethyl]amino}propyl)nicotinamide hydrochloride

Step A: Methyl 6-aminonicotinate

25 A suspension of 6-aminonicotinic acid (100 mg, 0.72 mmol) in MeOH (25 mL) was saturated with HCl (g) and the resulting mixture was stood at ambient temperature for 72 hrs, then concentrated *in vacuo* to give the desired ester.

Step B: Methyl 6-(tert-butoxycarbonylamino)nicotinate

30 To a stirred solution of methyl 6-aminonicotinate, as described above in Step A, (105 mg, 0.69 mmol) in DMF (3 mL) was added di-*tert*-butyl dicarbonate (158 mg, 0.72 mmol) and the reaction mixture was stirred at ambient temperature for 18 hrs, then concentrated *in vacuo* and partitioned between H_2O (10 mL) and EtOAc (20 mL). The aqueous layer was extracted further with EtOAc (2×20 mL). The
35 combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated *in*

vacuo. The crude product was purified by flash column chromatography on silica, eluting with a gradient of hexane - 20% to 50% EtOAc to yield the titled product.

Step C: Lithium 6-(*tert*-butoxycarbonylamino)nicotinate

5 To a stirred solution of methyl 6-(*tert*-butoxycarbonylamino)nicotinate, as described above in Step B, (36 mg, 0.14 mmol) in THF (5 mL) was added LiOH (1.5 mL of a 0.1 N solution in H₂O, 0.15 mmol) and the resulting mixture was stirred for 18 hrs. The pH of the solution was adjusted to ca. pH 7 with 1 N aqueous HCl and the solvents were removed under reduced pressure to
10 provide the desired salt.

Step D: (*S*)-6-*tert*-Butoxycarbonylamino-*N*-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide

15 (*S*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile hydrochloride (as described in Example 139) (18 mg, 0.031 mmol), lithium 6-(*tert*-butoxycarbonylamino)nicotinate (8 mg, 0.032 mmol), EDC (6 mg, 0.032 mmol), 1-hydroxybenzotriazole hydrate (4 mg, 0.032 mmol), and *N,N*-diisopropylethylamine (25 mL, 0.144 mmol) were
20 combined in DMF (1 mL) and the mixture was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The
25 crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 1% to 5% MeOH - 0.1% to 0.5% NH₄OH to yield the titled product.

Step E: (*S*)-6-Amino-*N*-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide hydrochloride

30 A solution (*S*)-6-*tert*-butoxycarbonylamino-*N*-(3-{[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide, as described above in Step D, (20 mg, 0.029 mmol) in EtOAc (5 mL)

at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo*, and the residue was partitioned between saturated aqueous Na₂CO₃ (3 mL) and CHCl₃ (20 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 1% to 5% MeOH - 0.1% to 0.5% NH₄OH to yield the
5 titled product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

FAB MS: 597 (MH⁺).

10 HRFABMS: 597.2475; calculated mass for C₃₂H₃₄ClN₈O₂ (MH⁺) = 597.2488

EXAMPLE 145

(3*S*)-4-[5-(1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl]-2-fluorobenzonitrile, diastereomer A,
15 hydrochloride

Step A: Benzyl 3-bromophenyl ether

To a stirred solution of 3-bromophenol (9.50 g, 54.9 mmol) in
20 degassed DMF (150 mL) at 0°C, under argon, was added Cs₂CO₃ (35.8 g, 109 mmol). The resulting mixture was stirred for 1 hr, then benzyl bromide (10.3 g, 60.2 mmol) was added and stirring was continued for 2 hrs at 0°C. The solvent was removed under reduced pressure, and the residue was partitioned between 20% aqueous NaOH (250 mL) and CHCl₃ (500 mL). The organic layer was dried over MgSO₄,
25 filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting first with two column volumes of hexane, then with hexane - 2% EtOAc to yield the desired product as a white solid.

Step B: (3-Benzyloxyphenyl)(3-chlorophenyl)methanol

30 To a stirred suspension of Rieke Mg (0.93 g, 38 mmol) in refluxing dry THF (15 mL), under argon, was added benzyl 3-bromophenyl ether, as described above in Step A, (9.0 g, 34 mmol) in dry THF (90 mL) dropwise, at a rate that maintained reflux with the heat source removed. The resulting mixture was heated to reflux for 1 hr, then allowed to cool to ambient temperature. The solution of Grignard
35 reagent was added dropwise to a stirred solution of 3-chlorobenzaldehyde in THF

(50 mL) at -78°C . The reaction mixture was stirred at -78°C for 1 hr, then quenched with saturated aqueous NH_4Cl (200 mL), allowed to warm to ambient temperature, and extracted with Et_2O (500 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with hexane - 7% EtOAc , to yield the titled product as a colorless oil.

Step C: (3-Benzoyloxyphenyl)(3-chlorophenyl)methyl azide

To a stirred solution of (3-benzoyloxyphenyl)(3-chlorophenyl)methanol, as described above in Step B, (4.0 g, 12.3 mmol) and diphenylphosphoryl azide (4.1 g, 14.9 mmol) in dry toluene (35 mL) at 0°C , was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.1 g, 13.8 mmol). The resulting mixture was allowed to warm to ambient temperature, and stirred under argon for 18 hrs, then washed with 5% hydrochloric acid (10 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane - 2% ethyl acetate to yield the product as a colorless oil.

Step D: (3-Benzoyloxyphenyl)(3-chlorophenyl)methylamine

(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl azide, as described above in Step C, (6.2 g, 17.7 mmol) was dissolved in dry THF (150 mL) and the solution was cooled to -70°C . Lithium aluminum hydride (21.2 mL of a 1.0 M solution in THF, 21.2 mmol) was added dropwise, then the reaction mixture was warmed to 0°C and stirred for 2 hrs. The reaction was quenched with EtOAc (0.75 mL), then water (0.75 mL), then 15% NaOH (0.75 mL), and finally water (2.2 mL). The resulting mixture was filtered, concentrated under reduced pressure and purified by flash column chromatography on silica, eluting with hexane - 15% EtOAc , to yield the titled product as a colorless oil.

Step E: (3*S*)-*N*-[(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl]-2-(*tert*-butoxycarbonylamino)-4-(methylmercapto) butyramide, diastereomers A & B

To (*S*)-*N*-(*tert*-butoxycarbonyl)methionine (1.60 g, 6.7 mmol) in dry CH_2Cl_2 (5 mL) under argon were added PYBOP (3.50 g, 6.7 mmol), (3-benzoyloxyphenyl)(3-chlorophenyl)methylamine, as described above in Step C, (2.0 g, 6.2 mmol), and *N,N*-diisopropylethylamine (1.2 mL, 6.9 mmol). The reaction mixture

was stirred for 2 hrs, then quenched with aqueous NaHCO₃ (20 mL), and extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with hexane - 20% ethyl acetate to yield a mixture
 5 (ca. 1:1) of diastereomeric amides as a white solid.

Step F: (3*S*)-*N*-[(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl]-2-(*tert*-butoxycarbonylamino)-4-(dimethylsulfonium)-butyramide iodide, diastereomers A & B

10 (3*S*)-*N*-[(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl]-2-(*tert*-butoxycarbonylamino)-4-(methylmercapto)butyramide, diastereomers A & B, as described above in Step E, (3.30 g, 5.94 mmol) was dissolved in iodomethane (20 L, 320 mmol) and the solution was stirred under argon for 18 hrs. The iodomethane was removed by distillation under reduced pressure to give the sulfonium salt
 15 diastereomers (ca. 1:1) as a yellow solid.

Step G: (3*S*)-{1-[(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl]-2-oxopyrrolidin-3-yl}carbamic acid *tert*-butyl ester, diastereomers A & B

20 (3*S*)-*N*-[(3-Benzoyloxyphenyl)(3-chlorophenyl)methyl]-2-(*tert*-butoxycarbonylamino)-4-(dimethylsulfonium)butyramide iodide, diastereomers A & B, as described above in Step F, (4.10 g, 5.94 mmol) was stirred in dry THF (90 mL), under argon, at 0°C and lithium bis(trimethylsilyl)amide (1.0 M in THF, 5.6 mL, 5.6 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 2 h, then quenched with saturated aqueous NH₄Cl (50 mL) and most of the THF was removed
 25 under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (25 mL) and CHCl₃ (75 mL). The aqueous layer was extracted further with CHCl₃ (2 × 25 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of hexane - 20% to 25%
 30 ethyl acetate to yield the mixture (ca. 1:1) of diastereomeric pyrrolidinones as a white solid.

Step H: (3*S*)-{1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-yl}carbamic acid *tert*-butyl ester, diastereomers A & B

35 To a solution of (3*S*)-{1-[(3-benzoyloxyphenyl)(3-chlorophenyl)

methyl]-2-oxopyrrolidin-3-yl} carbamic acid *tert*-butyl ester, diastereomers A & B, as described above in Step G, (1.30 g, 2.62 mmol) in EtOH (125 mL) and EtOAc (25 mL) was added 20% Pd(OH)₂ on carbon (250 mg) and acetic acid (5 mL) and the reaction mixture was stirred under an atmosphere of hydrogen (ca. 1 atm) at ambient temperature for 18 hrs. The mixture was filtered through a pad of celite, washing with EtOH, and the filtrate was concentrated *in vacuo* to give a crude product. This was purified by flash column chromatography on silica, eluting with a gradient of CHCl₃ - 20% to 30%, to yield the separated products, diastereomer A (higher R_F on silica gel) and diastereomer B (lower R_F on silica gel), as colorless oils.

10

Step I: (3*S*)-3-Amino-1-[(3-chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidine trifluoroacetate, diastereomer A

A solution of (3*S*)-{1-[(3-chlorophenyl)(3-hydroxyphenyl)-methyl]-2-oxopyrrolidin-3-yl} carbamic acid *tert*-butyl ester, diastereomer A, as described above in Step H, (480 mg, 1.15 mmol) in EtOAc (75 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine, which was purified by preparative HPLC on a Deltapak C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 60% CH₃CN to provide the titled product as a white foam.

20

Step J: (3*S*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile, diastereomer A, hydrochloride

(3*S*)-3-Amino-1-[(3-chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidine trifluoroacetate, diastereomer A, as described above in Step I, (95 mg, 0.221 mmol) and 1-(4-cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde, as described in Example 127, Step G, (56 mg, 0.244 mmol), were stirred in MeOH (1 mL) and *N,N*-diisopropylethylamine was added dropwise to adjust the mixture to ca. pH 5, as judged by wetted pH paper. The mixture was stirred for 1 hr at ambient temperature then NaCNBH₃ (17 mg, 0.27 mmol) was added, AcOH was added to adjust the mixture to about pH 5, and stirring was continued for 18 hrs. The MeOH was removed under reduced pressure, and the residue was partitioned between saturated aqueous NaHCO₃ (1 mL) and CHCl₃ (3 mL). The aqueous layer was extracted further with CHCl₃ (2 × 3 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified

35

by flash column chromatography on silica, eluting with CHCl_3 - 4% MeOH - 0.4% NH_4OH to yield the titled product as a white solid, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

5 Elemental analysis calculated for $\text{C}_{29}\text{H}_{25}\text{ClFN}_5\text{O}_2 \cdot 2 \text{HCl} \cdot 0.1 \text{H}_2\text{O} \cdot 0.85 \text{CH}_2\text{Cl}_2$:

C: 52.96; H: 4.30; N: 10.35

Found: C: 52.96; H: 4.18; N: 10.33

FAB MS: 530 (MH^+).

10

EXAMPLE 146

(3*S*)-2-Fluoro-4-[5-({1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]benzonitrile, diastereomer B, hydrochloride

15 Step A: (3*S*)-{1-[(3-Hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-yl}carbamic acid *tert*-butyl ester diastereomers A & B

To a solution of (3*S*)-{1-[(3-benzyloxyphenyl (3- chlorophenyl)-methyl]-2-oxopyrrolidin-3-yl}carbamic acid *tert*-butyl ester, diastereomers A & B, as described in Example 145, Step G, (1.20 g, 2.41 mmol) in EtOH (125 mL) and EtOAc (25 mL) was added 20% $\text{Pd}(\text{OH})_2$ on carbon (1.20 g) and the reaction mixture was shaken in a Parr hydrogenation apparatus under an atmosphere of hydrogen (ca. 50 atm) at ambient temperature for 3 days. The mixture was filtered through a pad of celite, washing with EtOH, and the filtrate was concentrated *in vacuo* to give a crude product. This was purified by flash column chromatography on silica, eluting with a gradient of CHCl_3 - 20% to 30%, to yield the separated products, diastereomer A (higher R_F on silica gel) and diastereomer B (lower R_F on silica gel), as colorless oils.

30 Step B: (3*S*)-3-Amino-1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidine trifluoroacetate, diastereomer B

A solution of (3*S*)-{1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-yl}carbamic acid *tert*-butyl ester, diastereomer B, as described above in Step A, (88 mg, 1.15 mmol) in EtOAc (15 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine, which was purified by preparative HPLC on a Deltapak C-18 column, eluting with a gradient of

0.1% aqueous trifluoroacetic acid - 5% to 60% CH₃CN to provide the titled product as a white foam.

- 5 Step C: (3*S*)-2-Fluoro-4-[5-({1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-benzonitrile, diastereomer B, hydrochloride
- 10 (3*S*)-3-Amino-1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidine trifluoroacetate, diastereomer B, as described above in Step B, (26 mg, 0.060 mmol) and 1-(4-cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde, as described in Example
- 15 127, Step G, (20 mg, 0.087 mmol), were stirred in MeOH (1 mL) and *N,N*-diisopropylethylamine was added dropwise to adjust the mixture to ca. pH 5, as judged by wetted pH paper. The mixture was stirred for 1 hr at ambient temperature then NaCNBH₃ (6 mg, 0.095 mmol) was added, AcOH was added to adjust the mixture to about pH 5, and stirring was continued for 18 hrs. The MeOH was removed under
- 20 reduced pressure, and the residue was partitioned between saturated aqueous NaHCO₃ (1 mL) and CHCl₃ (3 mL). The aqueous layer was extracted further with CHCl₃ (2 × 3 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CHCl₃ - 2% to 5% MeOH - 0.2% to 0.5% NH₄OH to
- yield the desired product, which was converted to the hydrochloride salt by treatment with HCl in EtOAc.

Elemental analysis calculated for C₂₉H₂₆FN₅O₂•2 HCl•1.2 H₂O:

- 25 Found: C: 59.11; H: 5.18; N: 11.89
 C: 59.14; H: 5.17; N: 11.61
 FAB MS: 496 (MH⁺).

EXAMPLE 147

- 30 (3*S*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile, diastereomer B, hydrochloride
- Following the procedures described in Example 145, but using (3*S*)-{1-[(3-chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-yl}carbamic acid
- 35 *tert*-butyl ester, diastereomer B (as described in Example 145, Step H) in place of

(3*S*)-{1-[(3-chlorophenyl)(3-hydroxy-phenyl)methyl]-2-oxopyrrolidin-3-yl} carbamic acid *tert*-butyl ester, diastereomer A, in Step I, the above-titled compound was obtained.

5 Elemental analysis calculated for C₂₉H₂₅ClFN₅O₂•2 HCl•H₂O•0.25 EtOAc:

C: 56.04; H: 4.86; N: 10.89

Found: C: 56.01; H: 5.19; N: 10.92

FAB MS: 530 (MH⁺).

10 EXAMPLE 148

(3*S*)-2-Fluoro-4-[5-({1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino} methyl)imidazol-1-ylmethyl]benzonitrile, diastereomer A, hydrochloride

15 Following the procedures described in Example 146, but using (3*S*)-{1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-yl} carbamic acid *tert*-butyl ester, diastereomer A, (as described in Example 146, Step A) in place of (3*S*)-{1-[(3-hydroxyphenyl)(phenyl) methyl]-2-oxopyrrolidin-3-yl} carbamic acid *tert*-butyl ester, diastereomer B in Step B, the above-titled compound was obtained.

20 Elemental analysis calculated for C₂₉H₂₆FN₅O₂•2 HCl•2.2 H₂O•0.15 EtOAc:

C: 57.22; H: 5.45; N: 11.27

Found: C: 57.19; H: 5.36; N: 11.28

FAB MS: 496 (MH⁺).

25 EXAMPLE 149

(3*R*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino} methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile, diastereomer A, hydrochloride

30 Following the procedures described in Example 145, but using (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in place of (*S*)-*N*-(*tert*-butoxycarbonyl)methionine, the above-titled compound was obtained.

Elemental analysis calculated for $C_{29}H_{25}ClFN_5O_2 \cdot 2 HCl \cdot 1.7 H_2O \cdot 0.2 C_6H_5CH_3$:

C: 56.08; H: 4.94; N: 10.76

Found: C: 56.07; H: 4.68; N: 10.78

FAB MS: 530 (MH^+).

5

EXAMPLE 150

(3*R*)-2-Fluoro-4-[5-({1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]benzonitrile, diastereomer B, hydrochloride

10 Following the procedures described in Example 146, but using (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in place of (*S*)-*N*-(*tert*-butoxycarbonyl)methionine, the above-titled compound was obtained.

Elemental analysis calculated for $C_{29}H_{26}FN_5O_2 \cdot 2 HCl \cdot 1.3 H_2O$:

15 C: 58.84; H: 5.21; N: 11.83

Found: C: 58.83; H: 5.19; N: 11.90

FAB MS: 496 (MH^+).

EXAMPLE 151

20

(3*R*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile, diastereomer B, hydrochloride

25 Following the procedures described in Example 147, but using (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in place of (*S*)-*N*-(*tert*-butoxycarbonyl)methionine, the above-titled compound was obtained.

Elemental analysis calculated for $C_{29}H_{25}ClFN_5O_2 \cdot 2 HCl \cdot 1.4 H_2O \cdot 0.3 C_6H_5CH_3$:

C: 56.96; H: 4.95; N: 10.68

30 Found: C: 56.93; H: 4.94; N: 10.72

FAB MS: 530 (MH^+).

35

EXAMPLE 152

(3*R*)-2-Fluoro-4-[5-({1-[(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]benzonitrile, diastereomer A, hydrochloride

5 Following the procedures described in Example 148, but using (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in place of (*S*)-*N*-(*tert*-butoxycarbonyl)methionine, the above-titled compound was obtained.

Elemental analysis calculated for C₂₉H₂₆FN₅O₂•2 HCl•2 H₂O•0.35 C₆H₅CH₃:

10 C: 59.40; H: 5.50; N: 11.01

Found: C: 59.44; H: 5.12; N: 10.68

FAB MS: 496 (MH⁺).

EXAMPLE 153

15

(*R*)-2-Fluoro-4-(5-{[1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride

Step A: 8-*tert*-Butoxycarbonylamino-2-naphthol

20

A mixture of 8-amino-2-naphthol (500 mg, 3.14 mmol) and di-*tert*-butyl dicarbonate (685 mg, 3.14 mmol) in CH₂Cl₂ (10 mL) and THF (5 mL) was stirred at 70°C for 18 hrs, then poured into saturated aqueous Na₂CO₃ (25 mL) and CH₂Cl₂ (75 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated
25 *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 0 to 7% ethyl acetate to yield the desired product as a light brown solid.

Step B: 7-Benzoyloxy-1-(*tert*-butoxycarbonylamino)naphthalene

30

A mixture of 8-*tert*-butoxycarbonylamino-2-naphthol, as described above in Step A, (93 mg, 0.36 mmol), benzyl bromide (64 mg, 0.37 mmol), and Cs₂CO₃ (146 mg, 0.45 mmol) in dry DMF (3 mL) was stirred, under argon, at ambient temperature for 18 hrs. The reaction mixture was poured into saturated aqueous NaHCO₃ (15 mL) and EtOAc (20 mL). The organic layer was dried over
35 Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by

flash column chromatography on silica, eluting with a gradient of hexane - 5 to 15% diethyl ether to yield the desired product as a pale solid.

Step C: 1-Amino-7-benzyloxynaphthalene

- 5 A solution of 7-benzyloxy-1-(*tert*-butoxycarbonylamino) naphthalene, as described above in Step B, (100 mg, 0.29 mmol) in EtOAc (10 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo*. The residue was partitioned between saturated aqueous Na₂CO₃ (5 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 10 mL). The
10 combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield the desired amine as a pale solid.

Step D: (*R*)-*N*-(7-Benzyloxynaphthalen-1-yl)-2-(*tert*-butoxycarbonylamino)-4-(methylmercapto)butyramide

- 15 To (*R*)-*N*-(*tert*-butoxycarbonyl)methionine (2.85 g, 12.0 mmol) in dry CH₂Cl₂ (5 mL) under argon were added PYBOP (6.26 g, 12.0 mmol), 1-amino-7-benzyloxynaphthalene, as described above in Step C, (3.0 g, 12.0 mmol), and *N,N*-diisopropylethylamine (2.12 mL, 12.2 mmol). The reaction mixture was stirred for 2 hrs, then partitioned between 10% aqueous citric acid (20 mL) and CH₂Cl₂ (150 mL).
20 The aqueous layer was extracted further with CH₂Cl₂ (2 × 150 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 2 column volumes of CH₂Cl₂, then CH₂Cl₂ - 5% ethyl acetate to yield the titled product.

- 25 Step E: (*R*)-*N*-(7-Benzyloxynaphthalen-1-yl)-2-(*tert*-butoxycarbonyl-amino)-4-(dimethylsulfonium)butyramide iodide
 (*R*)-*N*-(7-Benzyloxynaphthalen-1-yl)-2-(*tert*-butoxycarbonyl-amino)-4-(methylmercapto)butyramide, as described above in Step D, (4.69 g, 9.75 mmol) was dissolved in iodomethane (50 mL, 0.80 mol) and the solution was stirred under argon
30 for 18 hrs. The iodomethane was removed by distillation under reduced pressure to give the sulfonium salt as a yellow solid.

Step F: (*R*)-1-(7-Benzyloxynaphthalen-1-yl)-3-(*tert*-butoxycarbonyl-amino)-2-oxopyrrolidine

- 35 (*R*)-*N*-(7-Benzyloxynaphthalen-1-yl)-2-(*tert*-butoxycarbonyl-amino)-

4-(dimethylsulfonium)butyramide iodide, as described above in Step E, (6.40 g, 10.3 mmol) was stirred in dry THF (100 mL), under argon, at 0°C and lithium bis(trimethylsilyl)amide (1.0 M in THF, 9.76 mL, 9.76 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 2 h, then quenched with saturated aqueous NH₄Cl (75 mL) and most of the THF was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (75 mL) and CH₂Cl₂ (150 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 150 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 5% to 20% ethyl acetate to yield the pyrrolidinone as a white solid.

Step G: (R)-3-(tert-Butoxycarbonylamino)-1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidine

To a solution of (R)-1-(7-benzyloxynaphthalen-1-yl)-3-(tert-butoxycarbonylamino)-2-oxopyrrolidine, as described above in Step F, (1.00 g, 2.31 mmol) in EtOH (100 mL) and EtOAc (100 mL) was added 20% Pd(OH)₂ on carbon (150 mg) and the reaction mixture was stirred under an atmosphere of hydrogen (ca. 1 atm) at ambient temperature for 18 hrs. The mixture was filtered through a pad of celite, washing with EtOH, and the filtrate was concentrated *in vacuo* to give a crude product. This was purified by flash column chromatography on silica, eluting with a gradient of hexane - 50% to 75% EtOAc, to yield the titled product.

Step H: (R)-3-Amino-1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidine hydrochloride

A suspension of (R)-3-(tert-butoxycarbonylamino)-1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidine, as described above in Step G, (175 mg, 0.51 mmol) in EtOAc (10 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the amine hydrochloride as a white solid.

Step I: (R)-2-Fluoro-4-(5-{[1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-benzonitrile hydrochloride
(R)-3-Amino-1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidine

hydrochloride, as described above in Step H, (146 mg, 0.52 mmol) and 1-(4-cyano-

- 3-fluorobenzyl)-5-imidazolecarboxaldehyde, as described in Example 127, Step G, (126 mg, 0.55 mmol), were stirred in MeOH (2 mL) and *N,N*-diisopropylethylamine was added dropwise to adjust the mixture to ca. pH 5, as judged by wetted pH paper. The mixture was stirred for 1 hr at ambient temperature then NaCNBH₃ (43 mg, 0.68 mmol) was added, AcOH was added to adjust the mixture to about pH 5, and stirring was continued for 18 hrs. The reaction was quenched with saturated aqueous NaHCO₃ (2 mL) and most of the MeOH was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (3 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted further with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 1% to 6% MeOH - 0.1% to 0.6% NH₄OH to yield the titled product, which was converted to the hydrochloride salt with HCl in EtOAc.
- Elemental analysis calculated for C₂₆H₂₂FN₅O₂•3 HCl•0.2 MeOH•0.35 EtOAc:
C: 56.84; H: 4.94; N: 12.01
Found: C: 56.84; H: 5.34; N: 12.35
FAB MS: 456 (MH⁺).

EXAMPLE 154

- (*S*)-2-Fluoro-4-(5-{[1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile hydrochloride
- Following the procedures described in Example 153, but using (*S*)-*N*-(*tert*-butoxycarbonyl)methionine in place of (*R*)-*N*-(*tert*-butoxycarbonyl)methionine in Step D, the above-titled compound was obtained.

- Elemental analysis calculated for C₂₆H₂₂FN₅O₂•3 HCl•0.55 H₂O•0.45 EtOAc:
C: 56.07; H: 5.03; N: 11.76
Found: C: 56.08; H: 5.35; N: 11.82
FAB MS: 456 (MH⁺).

EXAMPLE 155

5 (3*R*)-2-Fluoro-4-[1-(5-{[1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-yl)eth-1-yl]benzonitrile, diastereomers A & B, hydrochloride

Step A: α,α -Dibromo-4-cyano-3-fluorotoluene

To a solution of 4-cyano-3-fluorotoluene, as described in Example 127, Step C, (4.0 g, 29.6 mmol) in carbon tetrachloride (250 mL) was added *N*-bromosuccinimide (10.5 g, 59.2 mmol) and 2,2'-azobisisobutyronitrile (490 mg, 3.0 mmol). The reaction mixture was heated to reflux under argon for 24 hrs, then cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with a gradient of hexane - 3% to 7% EtOAc, to yield the titled product as a yellow-brown solid.

15

Step B: 4-Cyano-3-fluorobenzaldehyde

To a solution of α,α -dibromo-4-cyano-3-fluorotoluene, as described above in Step A, (5.60 g, 19.1 mmol) in EtOH (255 mL) and water (45 mL) was added AgNO₃. The mixture was heated to reflux for 3 hrs, then stood at ambient temperature for 18 hrs, then the solid was removed by filtration and the filtrate was concentrated under reduced pressure to a volume of approximately 20 mL. Water (30 mL) was added, and the mixture was concentrated to dryness *in vacuo*. The residue was partitioned between saturated aqueous NaHCO₃ (20 mL) and CH₂Cl₂ (50 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dried for several days at ca. 0.5 mm Hg to yield the desired aldehyde as a pale solid.

20

25

Step C: 1-(4-Cyano-3-fluorophenyl)ethanol

To a solution of 4-cyano-3-fluorobenzaldehyde, as described above in Step B, (250 mg, 1.68 mmol) in THF, under argon, at -78°C was added MeMgBr dropwise (0.59 mL of a 3.0 M solution in Et₂O, 1.77 mmol). The reaction mixture was stirred at -78°C for 1 hr, then quenched with saturated aqueous NH₄Cl, allowed to warm to ambient temperature, and extracted with CH₂Cl₂ (2 × 40 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated

30

35

in vacuo. The residue was purified by silica gel chromatography, eluting with a gradient of hexane - 20% to 40% EtOAc, to yield the titled product as a white solid.

Step D: 4-(*tert*-Butyldimethylsilyloxymethyl)-1-(triphenylmethyl) imidazole
5 4-(Hydroxymethyl)-1-(triphenylmethyl)imidazole, as described in

Example 1, Step A, (1.97 g, 5.72 mmol) and 4-(dimethylamino)pyridine (280 mg, 2.29 mmol) were stirred in CH₂Cl₂ (15 mL) and *tert*-butyldimethylsilyl chloride (905 mg, 6.01 mmol) was added. After 1 min, triethylamine (0.88 mL, 6.31 mmol) was added dropwise over 3 min. The reaction mixture was stirred for 45 min, then
10 CH₂Cl₂ (150 mL) was added and the solution was washed with 0.1 N HCl (50 mL). The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with hexane - 30% EtOAc, to yield the titled product as a white solid.

15 Step E: 5-(*tert*-Butyldimethylsilyloxymethyl)-1-[1-(4-cyano-3-fluorophenyl)ethyl]imidazole

A mixture of 4-(*tert*-butyldimethylsilyloxymethyl)-1-(triphenylmethyl)imidazole, as described above in Step D, (485 mg, 1.07 mmol), 1-(4-cyano-3-fluorophenyl)ethanol, as described above in Step C, (160 mg, 0.969 mmol), and
20 *N,N*-diisopropylethylamine (0.219 mL, 1.26 mmol) in CH₂Cl₂ (12 mL) was cooled to -78°C, under argon. Trifluoromethanesulfonic anhydride (0.196 mL, 1.17 mmol) was added dropwise, and the mixture was stirred for 18 hrs while it slowly warmed to ambient temperature. Methanol (15 mL) was added and the CH₂Cl₂ was distilled off *in vacuo*. The resulting methanolic solution was heated to reflux for 3 hrs, then
25 concentrated *in vacuo* to give a residue which was partitioned between saturated aqueous Na₂CO₃ (10 mL) and CH₂Cl₂ (20 mL). The aqueous layer was extracted further with CH₂Cl₂ (20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a gradient of CH₂Cl₂ - 0% to 5% MeOH, to yield
30 the titled product as a pale foam.

Step F: 1-[1-(4-Cyano-3-fluorophenyl)ethyl]-5-(hydroxymethyl) imidazole

To a solution of 5-(*tert*-butyldimethylsilyloxymethyl)-1-[1-(4-cyano-3-fluorophenyl)ethyl]imidazole, as described above in Step E, (101 mg, 0.281 mmol) in
35 THF (2 mL) was added tetrabutylammonium fluoride (0.309 mL of a 1.0 M solution in

THF, 0.309 mmol) dropwise. The reaction mixture was stirred for 1 hr, then poured into saturated aqueous NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a gradient of CH₂Cl₂ - 0% to 10% MeOH, to yield the desired product as a pale solid.

Step G: 1-[1-(4-Cyano-3-fluorophenyl)ethyl]-5-imidazole-carboxaldehyde

To a solution of 1-[1-(4-cyano-3-fluorophenyl)ethyl]-5-(hydroxymethyl)imidazole, as described above in Step F, (60 mg, 0.245 mmol) in DMSO (1 mL) at ambient temperature was added triethylamine (0.136 mL, 0.979 mmol), then SO₃-pyridine complex (97 mg, 0.612 mmol). After 30 minutes, the reaction was poured into EtOAc (10 mL), washed with water (4 × 2 mL) and brine (2 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the aldehyde as a pale solid.

Step H: (3R)-2-Fluoro-4-[1-(5-{[1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-yl)eth-1-yl]benzonitrile, diastereomers A & B, hydrochloride

Following the procedures described in Example 153, but using 1-[1-(4-cyano-3-fluorophenyl)ethyl]-5-imidazolecarboxaldehyde (as described above in Step G) in place of 1-(4-cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde in Step I, the above-titled compound was obtained. The product was obtained as a ca. 1:1 mixture of two diastereomers.

Elemental analysis calculated for C₂₇H₂₄FN₅O₂•3 HCl•0.45 H₂O•0.45 EtOAc:

C: 56.92; H: 5.23; N: 11.53

Found: C: 56.91; H: 5.39; N: 11.59

FAB MS: 470 (MH⁺).

EXAMPLE 156

(R)-3-{[1-(4-Cyanobenzyl)-1H-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide hydrochloride

Step A: (R)-3-(tert-Butoxycarbonylamino)pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide

A mixture of (*R*)-3-(*tert*-butoxycarbonylamino)pyrrolidine, which is commercially available, (1.00 g, 5.37 mmol) and 1-adamantyl isocyanate (1.05 g, 5.93 mmol) in dry THF (30 mL) was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was crystallized from
5 CH₂Cl₂ - hexane to provide the desired urea.

Step B: (*R*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]-amino}
pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide hydrochloride
Following the procedures described in Example 1, but using (*R*)-3-
10 (*tert*-butoxycarbonylamino)pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide (as described above in Step A) in place of (*R*)-3-(*tert*-butoxycarbonylamino)-2-oxo-1-phenylpyrrolidine in Step I, the above-titled compound was obtained.

Elemental analysis calculated for C₂₇H₃₄N₆O•2 HCl•2.1 H₂O•0.25 EtOAc:
15 C: 56.86; H: 7.19; N: 14.21
Found: C: 56.90; H: 6.86; N: 14.17
FAB MS: 459 (MH⁺).

EXAMPLE 157

20 (*S*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide hydrochloride
Following the procedures described in Example 156, but using (*S*)-3-(*tert*-butoxycarbonylamino)pyrrolidine in place of (*R*)-3-(*tert*-butoxycarbonylamino)
25 pyrrolidine in Step A, the above-titled compound was obtained.

Elemental analysis calculated for C₂₇H₃₄N₆O•2 HCl•1.5 H₂O•0.05 CH₃CN:
C: 56.32; H: 6.90; N: 14.66
Found: C: 56.34; H: 6.70; N: 14.69
30 FAB MS: 459 (MH⁺).

EXAMPLE 158

(*R*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-
35 carboxylic acid (2,6-difluorophenyl)amide hydrochloride

Following the procedures described in Example 156, but using 2,6-difluorophenyl isocyanate in place of 1-adamantyl isocyanate in Step A, the above-titled compound was obtained.

5 Elemental analysis calculated for $C_{23}H_{22}F_2N_6O \cdot 2 HCl \cdot 0.05 H_2O \cdot 0.45 CHCl_3$:

C: 49.93; H: 4.39; N: 14.90

Found: C: 49.98; H: 4.37; N: 14.63

FAB MS: 437 (MH^+).

10 EXAMPLE 159

(*S*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (2,6-difluorophenyl)amide hydrochloride

15 Following the procedures described in Example 156, but using (*S*)-3-(*tert*-butoxycarbonylamino)pyrrolidine in place of (*R*)-3-(*tert*-butoxycarbonylamino)pyrrolidine, and 2,6-difluorophenyl isocyanate in place of 1-adamantyl isocyanate in Step A, the above-titled compound was obtained.

Elemental analysis calculated for $C_{23}H_{22}F_2N_6O \cdot 2 HCl \cdot 0.55 CHCl_3$:

20 C: 49.18; H: 4.30; N: 14.62

Found: C: 49.20; H: 4.32; N: 14.31

FAB MS: 437 (MH^+).

25 EXAMPLE 160

(*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile hydrochloride

Step A: Ethyl 5-(4-cyanobenzyl)nicotinate

30 Zinc dust (acid washed then dried *in vacuo*, 915 mg, 14 mmol) and 1,2-dibromoethane (132 mg, 0.7 mmol) were stirred in dry THF (7 mL) under argon at ambient temperature for 1 hr. A solution of 4-cyanobenzyl bromide (1.78 g, 9.1 mmol) in dry THF (8 mL) was added dropwise over 10 min and the resulting mixture was stirred for 4 hrs. Ethyl 5-bromonicotinate (1.61 g, 7.0 mmol) was added in one
35 portion, followed by $NiCl_2(PPh_3)_2$ (458 mg, 0.7 mmol) and stirring was continued

at ambient temperature for 18 hrs. Saturated aqueous NH_4Cl (25 mL) was added and the mixture was stirred for 2 hrs. The mixture was adjusted to $\text{pH} \approx 8$ by addition of saturated aqueous NaHCO_3 , and then extracted with EtOAc (2×100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*, and the residue was purified by silica gel chromatography, eluting with a gradient of hexane - 20% to 50% EtOAc, to yield the desired product as a pale solid.

Step B: Lithium 5-(4-cyanobenzyl)nicotinate

Ethyl 5-(4-cyanobenzyl)nicotinate, as described above in Step A, (1.06 g, 3.98 mmol) was dissolved in THF (30 mL) and H_2O (4.38 mL). 1.0 N aqueous lithium hydroxide (4.38 mL, 4.38 mmol) was added and the resulting mixture was stirred at ambient temperature for 18 hrs, then adjusted to pH 7 with 1.0 N aqueous HCl and concentrated to dryness *in vacuo* to give the titled lithium salt.

Step C: N-Methoxy-N-methyl-5-(4-cyanobenzyl)nicotinamide

Lithium 5-(4-cyanobenzyl)nicotinate, as described above in Step B, (502 mg, 2.06 mmol), *N,O*-dimethylhydroxylamine hydrochloride, (221 mg, 2.26 mmol), EDC (473 mg, 2.47 mmol), 1-hydroxybenzotriazole hydrate (278 mg, 2.06 mmol), and *N,N*-diisopropylethylamine (716 mL, 4.11 mmol) were combined in DMF (7 mL) and the mixture was stirred at ambient temperature for 18 hrs. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous Na_2CO_3 (50 mL) and EtOAc (100 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of EtOAc - 0% to 2% MeOH to yield the titled product.

Step D: 5-(4-Cyanobenzyl)nicotinaldehyde

To a solution of *N*-methoxy-*N*-methyl-5-(4-cyanobenzyl)nicotinamide, as described above in Step C, (1.86 g, 6.61 mmol) in dry THF (70 mL), at -78°C , under argon, was added DIBAL (5.3 mL of a 1.5 M solution in toluene, 7.95 mmol) dropwise over 10 min. The mixture was stirred at -78°C for 90 min, then an additional portion of DIBAL (2.6 mL of a 1.5 M solution in toluene, 3.9 mmol) was added dropwise. After a further 60 min at -78°C , the reaction mixture was quenched with

a solution of 5% HCl in 1:1 MeOH – H₂O (50 mL) and allowed to warm to –10°C. Saturated aqueous NaHCO₃ (100 mL) and 1.0 N aqueous NaOH (15 mL) were added, and the resulting mixture was extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated *in vacuo*, and the crude solid was purified by silica gel chromatography, eluting with EtOAc - 30% hexane, to yield the desired product as a crystalline solid.

Step E: (S)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile hydrochloride

(S)-3-Amino-1-(3-chlorobenzyl)-2-oxopyrrolidine hydrochloride (as described in Example 11) (57 mg, 0.22 mmol) and 5-(4-cyanobenzyl)nicotinaldehyde, as described above in Step D, (51 mg, 0.23 mmol), were stirred in MeOH (1 mL) and *N,N*-diisopropylethylamine was added dropwise to adjust the mixture to ca. pH 5, as judged by wetted pH paper. The mixture was stirred for 30 min at ambient temperature then NaCNBH₃ (16 mg, 0.26 mmol) was added, AcOH was added to adjust the mixture to about pH 5, and stirring was continued for 18 hrs. The reaction mixture was concentrated under reduced pressure, and the residual solution was partitioned between saturated aqueous NaHCO₃ (1 mL) and CH₂Cl₂ (3 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 3 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 0% to 5% MeOH - 0% to 0.5% NH₄OH to yield the titled product, which was converted to the hydrochloride salt with HCl in EtOAc.

Elemental analysis calculated for C₂₅H₂₃N₄OCl•2 HCl•0.35 EtOAc•0.4 H₂O:

C: 54.19; H: 5.03; N: 12.34

Found: C: 54.26; H: 5.00; N: 12.35

FAB MS: 431 (MH⁺).

EXAMPLE 161

(S)-4-{5-[(2-Oxo-1-pyridin-4-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

Following the procedures described in Example 137, but using 4-aminopyridine in place of 2-aminopyridine in Step B, the above-titled compound was obtained.

5 Elemental analysis calculated for $C_{21}H_{20}N_6O \cdot 3 HCl \cdot EtOAc \cdot 0.15 H_2O$:

C: 52.44; H: 5.51; N: 14.68

Found: C: 52.44; H: 5.57; N: 14.72

FAB MS: 373 (MH^+).

10

EXAMPLE 162

(*S*)-4-{5-[(2-Oxo-1-pyridin-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

15 Following the procedures described in Example 137, but using 3-aminopyridine in place of 2-aminopyridine in Step B, the above-titled compound was obtained.

Elemental analysis calculated for $C_{21}H_{20}N_6O \cdot 3 HCl \cdot 0.2 EtOAc \cdot 0.6 H_2O$:

C: 51.31; H: 5.10; N: 16.47

20 Found: C: 51.34; H: 5.45; N: 16.47

FAB MS: 373 (MH^+).

EXAMPLE 163

25 (*S*)-4-{5-[(2-Oxo-1-pyrazin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
benzonitrile trifluoroacetate

30 Following the procedures described in Example 137, but using aminopyrazine in place of 2-aminopyridine in Step B, and purifying the final product by HPLC on a C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH_3CN , the above-titled compound was obtained.

Elemental analysis calculated for $C_{20}H_{19}N_7O \cdot 2 CF_3CO_2H \cdot H_2O$:

C: 46.53; H: 3.74; N: 15.83

Found: C: 46.44; H: 3.51; N: 15.87

35 FAB MS: 374 (MH^+).

EXAMPLE 164

5 (*R,S*)-4-{5-[(2-Oxo-1-tetrahydrofuran-3-yl)pyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile hydrochloride

Following the procedures described in Example 137, but using (*R*)-3-aminotetrahydrofuran in place of 2-aminopyridine in Step B, the above-titled compound was obtained.

10 Elemental analysis calculated for $C_{20}H_{23}N_5O_2 \cdot 2 HCl \cdot 0.5 H_2O$:

C: 53.70; H: 5.86; N: 15.65

Found: C: 53.52; H: 6.01; N: 15.82

FAB MS: 366 (MH^+).

15 EXAMPLE 165

(*S*)-4-{5-[(2-Oxo-1-thiazol-2-yl)pyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile trifluoroacetate

20 Following the procedures described in Example 137, but using 2-aminothiazole in place of 2-aminopyridine in Step B, and purifying the final product by HPLC on a C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH_3CN , the above-titled compound was obtained.

Elemental analysis calculated for $C_{19}H_{18}N_6OS \cdot 2.2 CF_3CO_2H \cdot 0.6 H_2O$:

25 C: 43.91; H: 3.37; N: 13.13

Found: C: 43.91; H: 3.38; N: 13.05

FAB MS: 379 (MH^+).

EXAMPLE 166

30 (*S*)-4-{5-[(1-(4-Morpholinophenyl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile trifluoroacetate

Following the procedures described in Example 137, but using 4-morpholinoaniline in place of 2-aminopyridine in Step B, and purifying the final

product by HPLC on a C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH₃CN, the above-titled compound was obtained.

Elemental analysis calculated for C₂₆H₂₈N₆O₂•2.2 CF₃CO₂H•CHCl₃:

5 C: 45.62; H: 3.80; N: 10.16

Found: C: 45.65; H: 3.72; N: 10.10

FAB MS: 457 (MH⁺).

EXAMPLE 167

10

(R,S)-4-{5-[(1-(1-Benzylpyrrolidin-3-yl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile hydrochloride

Following the procedures described in Example 137, but using (R)-3-amino-1-benzylpyrrolidine in place of 2-aminopyridine in Step B, the above-titled
15 compound was obtained.

Elemental analysis calculated for C₂₇H₃₀N₆O•3 HCl•2.5 H₂O•0.45 CHCl₃:

C: 49.82; H: 5.84; N: 12.70

Found: C: 49.81; H: 5.81; N: 12.74

20 FAB MS: 455 (MH⁺).

EXAMPLE 168

25 (S)-4-{5-[(2-Oxo-1-quinolin-5-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile hydrochloride

Following the procedures described in Example 137, but using 5-aminoquinoline in place of 2-aminopyridine in Step B, the above-titled compound was obtained.

30 Elemental analysis calculated for C₂₅H₂₂N₆O•2.4 HCl•0.7 CHCl₃•1.7 H₂O:

C: 48.28; H: 4.48; N: 13.15

Found: C: 48.27; H: 4.48; N: 13.12

FAB MS: 423 (MH⁺).

35

EXAMPLE 169

(S)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methanoyl}imidazol-1-ylmethyl)benzonitrile trifluoroacetate

5

Step A: Sodium 1-(4-cyanobenzyl)-5-imidazolecarboxylate

The 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde, as described in Example 1, Step E, (100 mg, 0.487 mmol) and isobutylene (1 mL) were dissolved in *t*-butanol. Sodium chlorite (80% purity) (65 mg, 0.584 mmol) and sodium
 10 dihydrogen phosphate (67 mg, 0.487 mmol) were dissolved in water (1 mL) and added to the aldehyde solution. The clear solution gradually became pale yellow. After 2 hrs, a precipitate had formed. This was filtered and dried to give the title compound.

15

Step B: (S)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methanoyl}imidazol-1-ylmethyl)benzonitrile trifluoroacetate

(S)-3-Amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride (as described in Example 1I) (56 mg, 0.214mmol), sodium 1-(4-cyanobenzyl)-5-
 20 imidazolecarboxylate (as described in Step A) (69 mg, 0.279 mmol), 1-hydroxy-benzotriazole hydrate (43 mg, 0.322 mmol), EDC (62 mg, 0.322mmol) and *N,N*-diisopropylethylamine (93μL, 0.536 mmol) were combined in 1 mL DMF under Ar and were stirred overnight at ambient temperature. The crude mixture was applied onto a Gilson preparative HPLC system, and purified on a C-18 column, eluting with
 25 a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH₃CN, to afford the above-titled compound.

Elemental analysis calculated for C₂₃H₂₀ClN₅O₂•CF₃CO₂H•1.35 H₂O•0.35 EtOAc:

C:52.57; H:4.43; N:11.61

30 Found: C:52.58; H:4.18; N:11.58

FAB MS: 434 (MH⁺).

EXAMPLE 170

35 (R)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methanoyl}imidazol-1-ylmethyl)benzonitrile trifluoroacetate

Following the procedures described in Example 169, but using (*R*)-3-amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride, as described in Example 1H, in place of (*S*)-3-amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride in Step B, the above-titled compound was obtained.

Elemental analysis calculated for $C_{23}H_{20}ClN_5O_2 \cdot CF_3CO_2H \cdot 0.55 H_2O \cdot 0.35 EtOAc$:

C:53.86; H:4.26; N:11.90

Found: C:53.83; H:3.90; N:11.86

FAB MS: 434 (MH^+).

EXAMPLE 171

(3*S*)-4- {[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-(4-cyanophenyl)-2,3-dihydro-imidazo[2,1-*b*]thiazole, diastereomers A & B, trifluoroacetate

Step A: Ethyl 2-[2-(4-cyanophenyl)-2-oxo-ethylthio]-3*H*-imidazole-4-carboxylate

To a solution of 4-ethoxycarbonylimidazole-2-thiol (8.22 g, 47.8 mmol) and potassium carbonate (19.8 g, 143 mmol) in dry acetonitrile (100 mL) at ambient temperature was added 4-cyanophenacyl bromide (10.7 g, 47.8 mmol). The reaction mixture was stirred for 20 hrs, during which time a white precipitate formed. To the solution was added ice-water (100 mL). The resulting solid was filtered and washed with water (2 × 25 mL) to provide the title product as an off-white solid.

Step B: Ethyl 2-[2-(4-cyanophenyl)-2-hydroxy-1-ethylthio]-3*H*-imidazole-4-carboxylate

Ethyl 2-[2-(4-cyanophenyl)-2-oxo-ethylthio]-3*H*-imidazole-4-carboxylate, as described above in Step A, (6.91 g, 21.9 mmol) was suspended in methanol (50 mL). Sodium borohydride (829 mg, 21.9 mmol) was added in portions at 0°C, and the suspension was stirred until it became homogeneous (1 hr). The reaction was quenched by the addition of saturated aqueous ammonium chloride until hydrogen evolution ceased. The resulting precipitate was filtered and washed with water (2 × 25 mL) to provide the title product as a white.

Step C: Ethyl 3-(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole-5-carboxylate

To a solution of ethyl 2-[2-(4-cyanophenyl)-2-hydroxy-1-ethylthio]-3*H*-imidazole-4-carboxylate, as described above in Step B, (6.95 g, 21.9 mmol) and *N,N*-diisopropylethylamine (11.4 mL, 65.7 mmol) in methylene chloride (300 mL) and DMF (50 mL) was added di-*tert*-butyl dicarbonate (6.69 g, 30.7 mmol) at 0°C. The reaction mixture was stirred for 24 hrs, then methanesulfonic anhydride (7.63 g, 43.8 mmol) was added in one portion. The reaction mixture was stirred for 3 hrs at 25°C and 16 hrs at reflux, then poured into saturated aqueous sodium bicarbonate and extracted with methylene chloride (3 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by flash column chromatography, eluting with a gradient of 50 to 70% ethyl acetate in hexane, to provide the title compound as a yellow oil.

Step D: 3-(4-Cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole-5-carboxylic acid hydrochloride

To a solution of ethyl 3-(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole-5-carboxylate, as described above in Step C, (4.81 g, 16.1 mmol) in ethanol (10 mL) and methylene chloride (10 mL) at 0°C was added sodium hydroxide (10 M in water, 2.09 mL, 20.9 mmol). After stirring for 16 hours, the organic solvents were evaporated *in vacuo* at 25°C, and the water was removed by a stream of nitrogen. The crude product was acidified by the addition of hydrogen chloride (1 M in diethylether, 40 mL) and reconcentrated to provide the crude product as a white solid.

Step E: (3*S*)-4- {[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-(4-cyanophenyl)-2,3-dihydro-imidazo[2,1-*b*]thiazole, diastereomers A & B, trifluoroacetate

(*S*)-3-Amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride (as described in Example 1I) (56 mg, 0.214 mmol), 3-(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole-5-carboxylic acid hydrochloride (as described above in Step D) (115 mg, 0.375 mmol), 1-hydroxybenzotriazole hydrate (60 mg, 0.429 mmol), EDC (82 mg, 0.429 mmol) and *N,N*-diisopropylethylamine (360 µL, 2.06 mmol) were combined in DMF (1 mL) and stirred overnight at ambient temperature. The crude mixture was applied onto a Gilson preparative HPLC system, and purified on

a C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH₃CN, to afford the above-titled compound as an approximately 1:1 mixture of two diastereomers.

5 Elemental analysis calculated for $C_{24}H_{20}ClN_5O_2S \cdot CF_3CO_2H \cdot 0.6 H_2O \cdot 0.25 EtOAc$:
C:51.90; H:3.90; N:11.21
Found: C:51.93; H:3.56; N:11.20
FAB MS: 478 (MH⁺).

10 EXAMPLE 172

(3*R*)-4-{{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-(4-cyanophenyl)-2,3-dihydro-imidazo[2,1-*b*]thiazole, diastereomers A & B, trifluoroacetate

15 Following the procedures described in Example 171, but using (*R*)-3-amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride, as described in Example 1H, in place of (*S*)-3-amino-1-(3-chlorobenzyl)2-oxopyrrolidine hydrochloride in Step E, the above-titled compound was obtained.

20
Elemental analysis calculated for $C_{24}H_{20}ClN_5O_2S \cdot CF_3CO_2H \cdot 0.2 CH_3CN \cdot 0.3 EtOAc$:
C:52.90; H:3.86; N:11.62
Found: C:53.27; H:3.61; N:11.62
FAB MS: 478 (MH^+).

25

EXAMPLE 173

2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl}
benzonitrile hydrochloride

Step A: 1-(*tert*-Butoxycarbonyl)-4-[2-(*tert*-butoxycarbonylamino)ethyl]imidazole

To a stirred suspension of histamine dihydrochloride (23.6 g, 128 mmol) in MeOH (270 mL) was added di-*tert*-butyl dicarbonate (58.8 g, 269 mmol) in 35 MeOH (180 mL), dropwise. The resulting mixture was stirred at ambient temperature

for 18 hrs, then concentrated under reduced pressure. The residue was partitioned between H₂O (200 mL) and CH₂Cl₂ (700 mL), and the aqueous phase was adjusted to pH = 5.5 with 1.0 N aqueous HCl. After extraction, the CH₂Cl₂ layer was washed with H₂O (200 mL), then brine (200 mL), then dried over Na₂SO₄, filtered, and
5 concentrated *in vacuo*. The crude solid was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ - 0% to 3% MeOH to yield the titled product.

Step B: α,α -Dibromo-4-cyano-3-fluorotoluene

10 To a solution of 4-cyano-3-fluorotoluene, as described in Example 127, Step C, (4.0 g, 29.6 mmol) in carbon tetrachloride (250 mL) was added *N*-bromosuccinimide (10.5 g, 59.2 mmol) and 2,2'-azobisisobutyronitrile (490 mg, 3.0 mmol). The reaction mixture was heated to reflux under argon for 24 hrs, then cooled to room temperature, filtered, and concentrated under reduced pressure.
15 The residue was purified by silica gel chromatography, eluting with a gradient of hexane - 3% to 7% EtOAc, to yield the titled product as a yellow-brown solid.

Step C: 4-Cyano-3-fluorobenzaldehyde

20 To a solution of α,α -dibromo-4-cyano-3-fluorotoluene, as described above in Step B, (5.60 g, 19.1 mmol) in EtOH (255 mL) and water (45 mL) was added AgNO₃. The mixture was heated to reflux for 3 hrs, then stood at ambient temperature for 18 hrs, then the solid was removed by filtration and the filtrate was concentrated under reduced pressure to a volume of approximately 20 mL. Water (30 mL) was added, and the mixture was concentrated to dryness *in vacuo*. The residue
25 was partitioned between saturated aqueous NaHCO₃ (20 mL) and CH₂Cl₂ (50 mL). The aqueous layer was extracted further with CH₂Cl₂ (2 × 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was dried for several days at ca. 0.5 mm Hg to yield the desired aldehyde as a pale solid.

30

Step D: 4-Cyano-3-fluorobenzyl alcohol

To a stirred solution of 4-cyano-3-fluorobenzaldehyde, as described above in Step C, (620 mg, 4.16 mmol) in EtOH (30 mL) at 0°C was added NaBH₄ (157 mg, 4.16 mmol) in one portion. The reaction mixture was stirred at 0°C for 10

min, then 10% aqueous citric acid (10 mL) was added and the solvent was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (10 mL) and CH₂Cl₂ (30 mL). The aqueous layer was extracted further with CH₂Cl₂ (30 mL). The combined organic extracts were dried over MgSO₄,
5 filtered, and concentrated *in vacuo* to provide the titled compound as a white solid.

Step E: 5-[2-(*tert*-Butoxycarbonylamino)ethyl]-1-(4-cyano-3-fluorobenzyl)
imidazole

To a stirred solution of 4-cyano-3-fluorobenzyl alcohol, as described
10 above in Step D, (18.9 g, 125 mmol) and *N,N*-diisopropylethylamine (28.3 mL, 163 mmol) in CH₂Cl₂ (500 mL), at -78°C, under argon, was added trifluoromethane-sulfonic anhydride (21.1 mL, 125 mmol), dropwise. The reaction mixture was stirred at -78°C for 15 min, then a solution of 1-(*tert*-butoxycarbonyl)-4-[2-(*tert*-
15 butoxycarbonylamino)ethyl]imidazole, as described above in Step A, (39.0 g, 125 mmol) in CH₂Cl₂ (300 mL) was added slowly. The reaction mixture was allowed to warm slowly to ambient temperature, then stirred for 18 hrs, then saturated aqueous NaHCO₃ (250 mL) was added. After 4 hrs, the organic layer was extracted, washed with H₂O (2 × 200 mL), then brine (200 mL), then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chroma-
20 tography on silica, eluting with a gradient of CH₂Cl₂ - 0% to 5% MeOH - 0% to 0.5% NH₄OH, to yield the titled product.

Step F: 5-(2-Aminoethyl)-1-(4-cyano-3-fluorobenzyl)imidazole

A solution of 5-[2-(*tert*-butoxycarbonylamino)ethyl]-1-(4-cyano-3-
25 fluorobenzyl)imidazole, as described above in Step E, (41.8 g, 121 mmol) in EtOAc (500 mL) was saturated with HCl (g) at 0°C. The mixture was stood at 0°C for 10 min, then concentrated under reduced pressure. The residue was partitioned between saturated aqueous Na₂CO₃ (250 mL) and CH₂Cl₂ (500 mL). The aqueous layer was saturated with NaCl and extracted further with CHCl₃ (4 × 800 mL). The combined
30 organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the titled product as an oil.

Step G: 2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-
ylamino)ethyl]imidazol-1-ylmethyl}benzonitrile
35 hydrochloride

A mixture of 5-(2-aminoethyl)-1-(4-cyano-3-fluorobenzyl) imidazole, as described above in Step F, (105 mg, 0.43 mmol), 3-bromo-1-phenyl-2-pyrrolidinone (52 mg, 0.215 mmol), and K_2CO_3 (33 mg, 0.236 mmol) in dry DMF (0.5 mL) was stirred at ambient temperature for 24 hrs. The reaction mixture was
 5 poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (15 mL). The organic extract was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH_2Cl_2 - 1% to 6% MeOH - 0.1% to 0.6% NH_4OH to yield the desired product, which was converted to the hydrochloride salt by treatment with HCl in
 10 EtOAc.

Elemental analysis calculated for $C_{23}H_{24}FN_5O \cdot 2 HCl \cdot 1.3 H_2O \cdot 1.1 EtOAc$:

C:55.15; H:5.98; N:11.74

Found: C:55.19; H:5.58; N:11.70

15 FAB MS: 404 (MH^+).

EXAMPLE 174

4-(5- {[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]
 20 ethyl} imidazol-1-ylmethyl)-2-fluorobenzonitrile hydrochloride

Step A: 3-(tert-Butoxycarbonylamino)-2-oxopyrrolidine

3-Amino-2-oxopyrrolidine was prepared according to the procedure described by R. Pellegata *et al.*, *Synthesis*, **22**, 614-616 (1978). To a solution of 3-amino-2-oxopyrrolidine (6.96 g, 69.5 mmol) in DMF (30 mL) was added triethylamine (7.03 g, 69.5 mmol) and di-*tert*-butyl dicarboxylate (15.2 g, 69.5 mmol). The reaction mixture was stirred at ambient temperature for 18 hrs, then concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The layers were separated and the organic extract was washed with H_2O , then brine, then dried
 25 over Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the titled product.
 30

Step B: Methanesulfonic acid 4-bromo-3-methylphenyl ester

To a stirred solution of 4-bromo-3-methylphenol (9.87 g, 52.8 mmol) and triethylamine (10.70 g, 106 mmol) in CH_2Cl_2 (50 mL) at 0°C was added methane-

ulfonyl chloride (7.25 g, 63.3 mmol), dropwise. After 30 min at 0°C, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between saturated aqueous NaHCO₃ and EtOAc. The layers were separated and the organic extract was washed with aqueous NaHCO₃, then 3 N aqueous HCl, then brine, then dried over
5 Na₂SO₄, filtered, and concentrated *in vacuo* to provide the titled product.

Step C: Methanesulfonic acid 4-bromo-3-bromomethylphenyl ester

A mixture of methanesulfonic acid 4-bromo-3-methylphenyl ester, as described above in Step B, (14.3 g, 53.9 mmol), *N*-bromosuccinimide (14.4 g, 80.9
10 mmol), and 2,2'-azobisisobutyronitrile (1.34 g, 8.16 mmol) in CCl₄ was heated at 80°C for 18 hrs. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with a gradient of hexane - 5% to 20% EtOAc, to yield the titled product.

15 Step D: Methanesulfonic acid 4-bromo-3-(3-*tert*-butoxycarbonylamino-2-oxopyrrolidin-1-ylmethyl)phenyl ester

To a solution of 3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidine, as described above in Step A, (1.00 g, 4.99 mmol) in THF (10 mL) was added sodium hydride (230 mg of a 60% dispersion in oil, 5.75 mmol) in THF (5 mL), dropwise.
20 The resulting mixture was stirred for 30 min at ambient temperature, then a solution of methanesulfonic acid 4-bromo-3-bromomethylphenyl ester, as described above in Step C, (1.96 g, 5.70 mmol) in THF (6 mL) was added dropwise and stirring was continued for 2 hrs. The reaction was quenched with saturated aqueous NH₄Cl (3 mL), then concentrated *in vacuo*. The residue was partitioned between saturated
25 aqueous NaHCO₃ and EtOAc. The layers were separated and the organic extract was washed with H₂O, then brine, then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with CH₂Cl₂ - 5% MeOH, to yield the titled product.

30 Step E: 3-Amino-1-(2-bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidine hydrochloride

A solution of methanesulfonic acid 4-bromo-3-(3-*tert*-butoxycarbonyl-

mino-2-oxopyrrolidin-1-ylmethyl)phenyl ester, as described above in Step D, (720 mg, 1.55 mmol) in EtOAc (40 mL) at 0°C was saturated with HCl (g). After 15 min, the mixture was concentrated *in vacuo* to yield the above-titled amine hydrochloride.

- 5 Step F: 4-(5-{[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile hydrochloride
- 3-Amino-1-(2-bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidine, as described above in Step E, (640 mg, 1.12 mmol), 1-(4-cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde, as described above in Example 127, Step G, (333 mg, 1.45 mmol) were stirred in MeOH (8 mL) and the solution was acidified to pH = 5-6, as judged by wetted pH indicator paper, with acetic acid. Stirring was continued for 30 min, then NaCNBH₃ (118 mg, 1.88 mmol) was added. Stirring was continued for 18 hrs, then the reaction was quenched with saturated aqueous NaHCO₃ (2 mL) and most of the MeOH was removed under reduced pressure. The residual solution was partitioned between saturated aqueous NaHCO₃ (10 mL) and EtOAc (20 mL). The aqueous layer was extracted further with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica, eluting with a gradient of CH₂Cl₂ – 1% to 5% MeOH, to yield the desired product which was converted to the hydrochloride salt by treatment with HCl in ether.

Elemental analysis calculated for C₂₄H₂₃BrFN₅O₄S•2 HCl•2.5 CH₃CN•1.25 CH₂Cl₂:

C: 42.33; H: 4.11; N: 12.24

- 25 Found: C: 42.36; H: 4.03; N: 12.26

FAB MS: 576 (⁷⁹BrMH⁺).

EXAMPLE 175

- 30 (S)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine trifluoroacetate

Step A: (S)-1-[(2-Ethoxybenzyl)oxycarbonyl]-3-(trifluoroacetamido)pyrrolidine

- (*S*)-3-(Trifluoroacetamido)pyrrolidine hydrochloride (219 mg, 1.0 mmol) was added to a solution of 2-ethoxybenzyl 4-nitrophenyl carbonate (317 mg, 1.0 mmol) and 4-dimethylaminopyridine (120 mg, 1.0 mmol) in DMF (1 mL). The mixture was heated to 75°C for 1 hr then stirred overnight at ambient temperature.
- 5 The crude mixture was partitioned between H₂O and CHCl₃ and the CHCl₃ extract was dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide the titled product.

- Step B: (*S*)-3-Amino-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine
 (*S*)-1-[(2-Ethoxybenzyl)oxycarbonyl]-3-(trifluoroacetamido)
- 10 pyrrolidine, as described above in Step A, (360 mg, 1.0 mmol) was dissolved in MeOH (1 mL) and aqueous NaOH (2 mL of a 1.25 N solution, 2.5 mmol) and stirred at ambient temperature until starting amide disappeared, as judged by HPLC analysis. The reaction mixture was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the
- 15 titled product.

- Step C: (*S*)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine trifluoroacetate
- 20 (*S*)-3-Amino-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine, as described above in Step B, (260 mg, 0.98 mmol) was treated with Ti(*i*-PrO)₄ (0.3 mL, 1.0 mmol) and 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde, as described in Example 1, Step E, (200 mg, 0.97 mmole) for 2 hrs at ambient temperature. Ethanol (1 drop) and NaCNBH₃ (75 mg, 1.2 mmol) were added. The mixture was stirred for 4 hrs at ambient temperature then treated with additional NaCNBH₃ (50 mg, 0.8 mmol)
- 25 and stirred overnight. The reaction mixture was partitioned between aqueous NaOH and CH₂Cl₂. The CH₂Cl₂ extract was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude mixture was purified by preparative HPLC system on a C-18 column, eluting with a gradient of 0.1% aqueous trifluoroacetic acid - 5% to 95% CH₃CN, to afford the above-titled compound.

- 30
- Elemental analysis calculated for C₂₆H₃₁N₅O₃•2.35 CF₃CO₂H:
 C:50.56; H:4.36; N:9.60
Found: C:50.57; H:4.08; N:9.34

EXAMPLE 176

3-[[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine hydrochloride

5

Step A: 4-Nitrophenyl 2-trifluoromethoxybenzyl carbonate

A solution of 2-trifluoromethoxybenzyl alcohol (353 mg, 1.84 mmol) and 4-nitrophenyl chloroformate (409 mg, 2.03 mmol) in 7:1 THF/acetonitrile (5 mL), under a nitrogen atmosphere, are treated with pyridine (0.164 mL, 2.03 mmol) and the resulting suspension is stirred vigorously at ambient temperature for 18 hrs. The reaction is concentrated *in vacuo* to give a clear oil, which is purified by flash column chromatography on silica, eluting with hexanes - 10% EtOAc to yield the desired product.

15 Step B: 3-Amino-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine

To a solution of 3-(*tert*-butoxycarbonylamino)pyrrolidine (0.135 g, 0.724 mmol) in CH₂Cl₂ (4 mL) is added *N,N*-diisopropylethylamine (0.132 mL, 0.759 mmol) and 4-nitrophenyl 2-(trifluoromethoxy)benzyl carbonate, as described above in Step A, (284 mg, 0.796 mmol). The reaction is stirred at ambient temperature for 18 hrs and then is purified by flash column chromatography on silica, eluting with hexanes - 30% EtOAc to yield a white solid. This solid is treated with neat trifluoroacetic acid and is isolated as the free base form upon partitioning with dilute Na₂CO₃ and CH₂Cl₂. The titled product is isolated by drying (Na₂SO₄) and concentrating to a yellow oil.

25

Step C: 4-Bromo-2-methylimidazole-5-carboxaldehyde

4-Bromo-5-hydroxymethyl-2-methylimidazole is prepared according to the procedure described by S. P. Watson, *Synthetic Communications*, **22**, 2971-2977 (1992). A solution of 4-bromo-5-hydroxymethyl-2-methylimidazole (4.18 g, 21.9 mmol) is refluxed with manganese dioxide (16.1 g) in 1:1 CH₂Cl₂:dioxane (200 mL) for 16 hrs. The cooled reaction is filtered through celite and is concentrated to yield the title compound as a pale yellow solid.

30

Step D: 4-Bromo-1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde

4-Cyanobenzylbromide (1.05 g, 5.39 mmol) is added to a solution of 4-bromo-2-methylimidazole-5-carboxaldehyde, as described above in Step C, (1.02 g, 5.39 mmol) in dimethylacetamide (15 mL). The solution is cooled to -10°C and powdered potassium carbonate (0.745 g, 5.39 mmol) is added. The reaction mixture is stirred at -10°C for 2 hrs, and a further 4 hrs at 20°C. The reaction mixture is diluted with water and extracted with ethyl acetate. The organic phase is washed with water, then brine, and is dried over MgSO₄. Solvent evaporation yields the titled product.

10 **Step E:** 1-(4-Cyanobenzyl)-2-methylimidazole-5-carboxaldehyde
A solution of 4-bromo-1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde, as described above in Step D, (1.33 g, 4.37 mmol) and imidazole (0.600 g, 8.74 mmol) in 1:1 ethyl acetate-alcohol (150 mL) is stirred with 10% palladium on carbon (0.020 g) under 1 atm hydrogen. After 2 hrs, the reaction is
15 filtered through celite and is concentrated *in vacuo* to give the title compound.

Step F: 3-[[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine hydrochloride

Following the procedures described in Example 1, Step J, but using 3-amino-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine (as described above in Step B) in place of (*R*)-3-amino-2-oxo-1-phenylpyrrolidine, and 1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde (as described above in Step E) in place of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde, the above-titled compound is obtained.

25 EXAMPLE 177

In vitro inhibition of Ras farnesyl transferase

Transferase Assays. Isoprenyl-protein transferase activity assays are carried out at 30°C unless noted otherwise. A typical reaction contains (in a final volume of 50 µL): [³H]farnesyl diphosphate, Ras protein, 50 mM HEPES, pH 7.5, 5 mM MgCl₂, 5 mM dithiothreitol, 10 µM ZnCl₂, 0.1% polyethyleneglycol (PEG) (15,000-20,000 mw) and isoprenyl-protein transferase. The FPTase employed in the assay is prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) *Biochemistry* 32:5167-5176. After thermally pre-equilibrating the assay

mixture in the absence of enzyme, reactions are initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions are allowed to stand for 15 m (to complete the precipitation process). After adding 2 mL of 100% ethanol, the reactions are vacuum-filtered through Whatman GF/C filters. Filters are washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801 scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. Substrate concentrations for inhibitor IC_{50} determinations are as follows: FTase, 650 nM Ras-CVLS (SEQ.ID.NO.: 25), 100 nM farnesyl diphosphate.

The compounds of the instant invention are tested for inhibitory activity against human FPTase by the assay described above.

The compounds of the instant invention described in the above Examples 1-175 were tested for inhibitory activity against human FPTase by the assay described above and were found to have an IC_{50} of $\leq 10 \mu M$.

EXAMPLE 178

Modified In vitro GGTase inhibition assay

The modified geranylgeranyl-protein transferase inhibition assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 μL): [3H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM $MgCl_2$, 10 μM $ZnCl_2$, 0.1% PEG (15,000-20,000 mw), 2 mM dithiothreitol, and geranylgeranyl-protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Patent No. 5,470,832, incorporated by reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 2). Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 μL of a 3 mg/mL suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5%

BSA. The quenched reactions are allowed to stand for 2 hours before analysis on a Packard TopCount scintillation counter.

For inhibition studies, assays are run as described above, except inhibitors are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay mixture. IC₅₀ values are determined with Ras peptide near K_M concentrations. Enzyme and substrate concentrations for inhibitor IC₅₀ determinations are as follows: 75 pM GGTase-I, 1.6 mM Ras peptide, 100 nM geranylgeranyl diphosphate.

The compounds of the instant invention, including those compounds described in the above Examples 1-176, are tested for inhibitory activity against human GGTase-type I by the assay described above.

EXAMPLE 179

15 Cell-based in vitro ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. *et al.*, Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labeled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400 µCi [³⁵S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 mg/ml aprotinin/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immuno-precipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 µl of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immuno-precipitates are washed four times with IP buffer (20 mM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100/0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and

nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 180

5

Cell-based in vitro growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-ras, v-raf, or v-mos oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

EXAMPLE 181

Construction of SEAP reporter plasmid pDSE100

The SEAP reporter plasmid, pDSE100 was constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is derived from the plasmid pSEAP2-Basic (Clontech, Palo Alto, CA). The plasmid pCMV-RE-AKI was constructed by Deborah Jones (Merck) and contains 5 sequential copies of the 'dyad symmetry response element' cloned upstream of a 'CAT-TATA' sequence derived from the cytomegalovirus immediate early promoter. The plasmid also contains a bovine growth hormone poly-A sequence.

The plasmid, pDSE100 was constructed as follows. A restriction fragment encoding the SEAP coding sequence was cut out of the plasmid pSEAP2-

Basic using the restriction enzymes EcoR1 and HpaI. The ends of the linear DNA fragments were filled in with the Klenow fragment of E. coli DNA Polymerase I. The 'blunt ended' DNA containing the SEAP gene was isolated by electrophoresing the digest in an agarose gel and cutting out the 1694 base pair fragment. The vector
5 plasmid pCMV-RE-AKI was linearized with the restriction enzyme Bgl-II and the ends filled in with Klenow DNA Polymerase I. The SEAP DNA fragment was blunt end ligated into the pCMV-RE-AKI vector and the ligation products were transformed into DH5-alpha E. coli cells (Gibco-BRL). Transformants were screened for the proper insert and then mapped for restriction fragment orientation. Properly
10 oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid contains the SEAP coding sequence downstream of the DSE and CAT-TATA promoter elements and upstream of the BGH poly-A sequence.

15 Alternative Construction of SEAP reporter plasmid, pDSE101

The SEAP repotrer plasmid, pDSE101 is also constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is derived from plasmid pGEM7zf(-)/SEAP.

The plasmid pDSE101 was constructed as follows: A restriction
20 fragment containing part of the SEAP gene coding sequence was cut out of the plasmid pGEM7zf(-)/SEAP using the restriction enzymes Apa I and KpnI. The ends of the linear DNA fragments were chewed back with the Klenow fragment of E. coli DNA Polymerase I. The "blunt ended" DNA containing the truncated SEAP gene was isolated by electrophoresing the digest in an agarose gel and cutting out the
25 1910 base pair fragment. This 1910 base pair fragment was ligated into the plasmid pCMV-RE-AKI which had been cut with Bgl-II and filled in with E. coli Klenow fragment DNA polymerase. Recombinant plasmids were screened for insert orientation and sequenced through the ligated junctions. The plasmid pCMV-RE-AKI is derived from plasmid pCMVIE-AKI-DHFR (Whang , Y., Silberklang, M., Morgan,
30 A., Munshi, S., Lenny, A.B., Ellis, R.W., and Kieff, E. (1987) J. Virol., 61, 1796-1807) by removing an EcoRI fragment containing the DHFR and Neomycin markers. Five copies of the fos promoter serum response element were inserted as described previously (Jones, R.E., Defeo-Jones, D., McAvoy, E.M., Vuocolo, G.A., Wegrzyn, R.J., Haskell, K.M. and Oliff, A. (1991) *Oncogene*, 6, 745-751) to create plasmid
35 pCMV-RE-AKI.

The plasmid pGEM7zf(-)/SEAP was constructed as follows. The SEAP gene was PCR'd, in two segments from a human placenta cDNA library (Clontech) using the following oligos.

5 Sense strand N-terminal SEAP : 5' GAGAGGGAATTCTGGGCCCTTCCTGCAT
GCTGCTGCTGCTGCTGCTGCTGGGC 3' (SEQ.ID.NO.:3)

Antisense strand N-terminal SEAP: 5' GAGAGAGCTCGAGGTAAACCCGGGT
GCGCGGCGTCGGTGGT 3' (SEQ.ID.NO.:4)

10

Sense strand C-terminal SEAP: 5' GAGAGAGTCTAGAGTTAACCCGTGGTCC
CCGCGTTGCTTCCT 3' (SEQ.ID.NO.:5)

Antisense strand C-terminal SEAP: 5' GAAGAGGAAGCTTGGTACCGCCACTG
15 GGCTGTAGGTGGTGGCT 3' (SEQ.ID.NO.:6)

The N-terminal oligos (SEQ.ID.NO.: 3 and SEQ.ID.NO.: 4) were used to generate a 1560 bp N-terminal PCR product that contained EcoRI and HpaI restriction sites at the ends. The Antisense N-terminal oligo (SEQ.ID.NO.: 4) introduces an internal translation STOP codon within the SEAP gene along with the HpaI site. The
20 C-terminal oligos (SEQ.ID.NO.: 5 and SEQ.ID.NO.: 6) were used to amplify a 412 bp C-terminal PCR product containing HpaI and HindIII restriction sites. The sense strand C-terminal oligo (SEQ.ID.NO.: 5) introduces the internal STOP codon as well as the HpaI site. Next, the N-terminal amplicon was digested with EcoRI and HpaI
25 while the C-terminal amplicon was digested with HpaI and HindIII. The two fragments comprising each end of the SEAP gene were isolated by electrophoresing the digest in an agarose gel and isolating the 1560 and 412 base pair fragments. These two fragments were then co-ligated into the vector pGEM7zf(-) (Promega) which had been restriction digested with EcoRI and HindIII and isolated on an agarose gel. The
30 resulting clone, pGEM7zf(-)/SEAP contains the coding sequence for the SEAP gene from amino acids.

Construction of a constitutively expressing SEAP plasmid pCMV-SEAP-A

An expression plasmid constitutively expressing the SEAP protein
35 was created by placing the sequence encoding a truncated SEAP gene downstream

of the cytomegalovirus (CMV) IE-1 promoter. The expression plasmid also includes the CMV intron A region 5' to the SEAP gene as well as the 3' untranslated region of the bovine growth hormone gene 3' to the SEAP gene.

The plasmid pCMVIE-AKI-DHFR (Whang, Y., Silberklang, M., Morgan, A., Munshi, S., Lenny, A.B., Ellis, R.W., and Kieff, E. (1987) *J. Virol.*, 61:1796-1807) containing the CMV immediate early promoter was cut with EcoRI generating two fragments. The vector fragment was isolated by agarose electrophoresis and religated. The resulting plasmid is named pCMV-AKI. Next, the cytomegalovirus intron A nucleotide sequence was inserted downstream of the CMV IE1 promoter in pCMV-AKI. The intron A sequence was isolated from a genomic clone bank and subcloned into pBR322 to generate plasmid p16T-286. The intron A sequence was mutated at nucleotide 1856 (nucleotide numbering as in Chapman, B.S., Thayer, R.M., Vincent, K.A. and Haigwood, N.L., *Nuc.Acids Res.* 19, 3979-3986) to remove a SacI restriction site using site directed mutagenesis. The mutated intron A sequence was PCR'd from the plasmid p16T-287 using the following oligos.

Sense strand: 5' GGCAGAGCTCGTTTAGTGAACCGTCAG 3' (SEQ.ID.NO.: 7)

Antisense strand: 5' GAGAGATCTCAAGGACGGTGACTGCAG 3'
(SEQ.ID.NO.: 8)

These two oligos generate a 991 base pair fragment with a SacI site incorporated by the sense oligo and a Bgl-II fragment incorporated by the antisense oligo. The PCR fragment is trimmed with SacI and Bgl-II and isolated on an agarose gel. The vector pCMV-AKI is cut with SacI and Bgl-II and the larger vector fragment isolated by agarose gel electrophoresis. The two gel isolated fragments are ligated at their respective SacI and Bgl-II sites to create plasmid pCMV-AKI-InA.

The DNA sequence encoding the truncated SEAP gene is inserted into the pCMV-AKI-InA plasmid at the Bgl-II site of the vector. The SEAP gene is cut out of plasmid pGEM7zf(-)/SEAP (described above) using EcoRI and HindIII. The fragment is filled in with Klenow DNA polymerase and the 1970 base pair fragment isolated from the vector fragment by agarose gel electrophoresis. The pCMV-AKI-InA vector is prepared by digesting with Bgl-II and filling in the ends with Klenow DNA polymerase. The final construct is generated by blunt end ligating the SEAP fragment into the pCMV-AKI-InA vector. Transformants were screened for the

proper insert and then mapped for restriction fragment orientation. Properly oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid, named pCMV-SEAP-A (deposited in the ATCC under Budapest Treaty on August 27, 1998, and designated ATCC), contains a modified SEAP sequence downstream of the cytomegalovirus immediately early promoter IE-1 and intron A sequence and upstream of the bovine growth hormone poly-A sequence. The plasmid expresses SEAP in a constitutive manner when transfected into mammalian cells.

10 Alternative construction of a constitutively expressing SEAP plasmid pCMV-SEAP-B

An expression plasmid constitutively expressing the SEAP protein can be created by placing the sequence encoding a truncated SEAP gene downstream of the cytomegalovirus (CMV) IE-1 promoter and upstream of the 3' untranslated region of the bovine growth hormone gene.

15 The plasmid pCMVIE-AKI-DHFR (Whang, Y., Silberklang, M., Morgan, A., Munshi, S., Lenny, A.B., Ellis, R.W., and Kieff, E. (1987) J. Virol., 61:1796-1807) containing the CMV immediate early promoter and bovine growth hormone poly-A sequence can be cut with EcoRI generating two fragments. The vector fragment can be isolated by agarose electrophoresis and religated. The resulting plasmid is named pCMV-AKI. The DNA sequence encoding the truncated SEAP gene can be inserted into the pCMV-AKI plasmid at a unique Bgl-II in the vector. The SEAP gene is cut out of plasmid pGEMzf(-)/SEAP (described above) using EcoRI and HindIII. The fragments are filled in with Klenow DNA polymerase and the 1970 base pair fragment is isolated from the vector fragment by agarose gel electrophoresis. The pCMV-AKI vector is prepared by digesting with Bgl-II and filling in the ends with Klenow DNA polymerase. The final construct is generated by blunt end ligating the SEAP fragment into the vector and transforming the ligation reaction into E. coli DH5a cells. Transformants can then be screened for the proper insert and mapped for restriction fragment orientation. Properly oriented recombinant constructs would be sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid, named pCMV-SEAP-B contains a modified SEAP sequence downstream of the cytomegalovirus immediate early promoter, IE1, and upstream of a bovine growth hormone poly-A sequence. The plasmid would express SEAP in a constitutive manner when transfected into mammalian cells.

Cloning of a Myristylated viral-H-*ras* expression plasmid pSMS600

A DNA fragment containing viral-H-*ras* can be PCR'd from plasmid "HB-11 (deposited in the ATCC under Budapest Treaty on August 27, 1997, and designated ATCC 209,218) using the following oligos.

Sense strand:

5'TCTCCTCGAGGCCACCATGGGGAGTAGCAAGAGCAAGCCTAAGGACCC
CAGCCAGCGCCGGATGACAGAATACAAGCTTGTGGTGG 3'. (SEQ.ID.NO.:

9)

Antisense:

5'CACATCTAGATCAGGACAGCACAGACTTGCAGC 3'.

(SEQ.ID.NO.: 10)

A sequence encoding the first 15 aminoacids of the v-src gene, containing a myristylation site, is incorporated into the sense strand oligo. The sense strand oligo also optimizes the 'Kozak' translation initiation sequence immediately 5' to the ATG start site. To prevent prenylation at the viral-*ras* C-terminus, cysteine 186 would be mutated to a serine by substituting a G residue for a C residue in the C-terminal antisense oligo. The PCR primer oligos introduce an XhoI site at the 5' end and a XbaI site at the 3' end. The XhoI-XbaI fragment can be ligated into the mammalian expression plasmid pCI (Promega) cut with XhoI and XbaI. This results in a plasmid, pSMS600, in which the recombinant myr-viral-H-*ras* gene is constitutively transcribed from the CMV promoter of the pCI vector.

Cloning of a viral-H-*ras*-CVLL expression plasmid pSMS601

A viral-H-*ras* clone with a C-terminal sequence encoding the amino acids CVLL can be cloned from the plasmid "HB-11" by PCR using the following oligos.

Sense strand:

5'TCTCCTCGAGGCCACCATGACAGAATACAAGCTTGTGGTGG-3'

(SEQ.ID.NO.: 11)

Antisense strand:

5'CACTCTAGACTGGTGTCTCAGAGCAGCACACACTTGCAGC-3' (SEQ.ID.NO.: 12)

5 The sense strand oligo optimizes the 'Kozak' sequence and adds an
XhoI site. The antisense strand mutates serine 189 to leucine and adds an XbaI site.
The PCR fragment can be trimmed with XhoI and XbaI and ligated into the XhoI-
XbaI cut vector pCI (Promega). This results in a plasmid, pSMS601, in which the
mutated viral-H-*ras*-CVLL gene is constitutively transcribed from the CMV promoter
10 of the pCI vector.

Cloning of cellular-H-*ras*-Leu61 expression plasmid pSMS620

15 The human cellular-H-*ras* gene can be PCRed from a human cerebral
cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:

5'-GAGAGAATTCGCCACCATGACGGAATATAAGCTGGTGG-3'
(SEQ.ID.NO.: 13)

20 Antisense strand:

5'-GAGAGTCGACGCGTCAGGAGAGCACACACTTGC-3' (SEQ.ID.NO.: 14)

25 The primers will amplify a c-H-Ras encoding DNA fragment with the
primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at
the N-terminus and a Sal I site at the C-terminal end. After trimming the ends of the
PCR product with EcoRI and Sal I, the c-H-*ras* fragment can be ligated into an
EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glutamine-61
to a leucine can be accomplished using the manufacturer's protocols and the
following oligonucleotide:

30 5'-CCGCCGGCCTGGAGGAGTACAG-3' (SEQ.ID.NO.: 15)

35 After selection and sequencing for the correct nucleotide substitution,
the mutated c-H-*ras*-Leu61 can be excised from the pAlter-1 vector, using EcoRI and
Sal I, and be directly ligated into the vector pCI (Promega) which has been digested

with EcoRI and Sal I. The new recombinant plasmid, pSMS620, will constitutively transcribe c-H-*ras*-Leu61 from the CMV promoter of the pCI vector.

Cloning of a c-N-*ras*-Val-12 expression plasmid pSMS630

5 The human c-N-*ras* gene can be PCR'd from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:

5'-GAGAGAATTCGCCACCATGACTGAGTACAAACTGGTGG-3'
10 (SEQ.ID.NO.: 16)

Antisense strand:

5'-GAGAGTCGACTTGTTACATCACCACACATGGC-3' (SEQ.ID.NO.: 17)

15 The primers will amplify a c-N-Ras encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I site at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-N-*ras* fragment can be ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glycine-12 to
20 a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTTGGAGCAGTTGGTGTGGG-3' (SEQ.ID.NO.: 18)

25 After selection and sequencing for the correct nucleotide substitution, the mutated c-N-*ras*-Val-12 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new recombinant plasmid, pSMS630, will constitutively transcribe c-N-*ras*-Val-12 from the CMV promoter of the pCI vector.

30

Cloning of a c-K4B-*ras*-Val-12 expression plasmid pSMS640

The human c-K4B-*ras* gene can be PCR'd from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

35 Sense strand:

5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3'
(SEQ.ID.NO.: 19)

Antisense strand:

5'-CTCTGTCGACGTATTTACATAATTACACACTTTGTC-3' (SEQ.ID.NO.: 20)

5 The primers will amplify a c-K4B-Ras encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, a KpnI site at the N-terminus and a Sal I site at the C-terminal end. After trimming the ends of the PCR product with Kpn I and Sal I, the c-K4B-*ras* fragment can be ligated into a KpnI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to
10 a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 21)

15 After selection and sequencing for the correct nucleotide substitution, the mutated c-K4B-*ras*-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with KpnI and Sal I. The new recombinant plasmid will constitutively
20 transcribe c-K4B-*ras*-Val-12 from the CMV promoter of the pCI vector.

Cloning of c-K-*ras*4A-Val-12 expression plasmid pSMS650

The human c-K4A-*ras* gene can be PCR'd from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

25 Sense strand:

5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3'
(SEQ.ID.NO.: 22)

Antisense strand:

30 5'-CTCTGTCGACAGATTACATTATAATGCATTTTTTAATTTTCACAC-3'
(SEQ.ID.NO.: 23)

 The primers will amplify a c-K4A-Ras encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, a KpnI site
35 at the N-terminus and a Sal I site at the C-terminal end. After trimming the ends of

the PCR product with Kpn I and Sal I, the c-K-ras4A fragment can be ligated into a KpnI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5

5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 24)

After selection and sequencing for the correct nucleotide substitution, the mutated c-K4A-*ras*-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with KpnI and Sal I. The new recombinant plasmid, pSMS650, will constitutively transcribe c-K4A-*ras*-Val-12 from the CMV promoter of the pCI vector.

15 SEAP assay

Human C33A cells (human epithelial carcinoma - ATTC collection) are seeded in 10cm tissue culture plates in DMEM + 10% fetal calf serum + 1X Pen/Strep + 1X glutamine + 1X NEAA. Cells are grown at 37°C in a 5% CO₂ atmosphere until they reach 50 -80% of confluency. The transient transfection is performed by the CaPO₄ method (Sambrook et al., 1989). Thus, expression plasmids for H-*ras*, N-*ras*, K-*ras*, Myr-*ras* or H-*ras*-CVLL are co-precipitated with the DSE-SEAP reporter construct. (A *ras* expression plasmid is not included when the cell is transfected with the pCMV-SEAP plasmid.) For 10cm plates 600µl of CaCl₂-DNA solution is added dropwise while vortexing to 600µl of 2X HBS buffer to give 1.2ml of precipitate solution (see recipes below). This is allowed to sit at room temperature for 20 to 30 minutes. While the precipitate is forming, the media on the C33A cells is replaced with DMEM (minus phenol red; Gibco cat. No. 31053-028)+ 0.5% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and nonessential aminoacids). The CaPO₄-DNA precipitate is added dropwise to the cells and the plate rocked gently to distribute. DNA uptake is allowed to proceed for 5-6 hrs at 37°C under a 5% CO₂ atmosphere.

Following the DNA incubation period, the cells are washed with PBS and trypsinized with 1ml of 0.05% trypsin. The 1 ml of trypsinized cells is diluted into 10ml of phenol red free DMEM + 0.2% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and NEAA). Transfected cells are plated in a 96 well micro-

35

titer plate (100ml/well) to which drug, diluted in media, has already been added in a volume of 100 μ l. The final volume per well is 200 μ l with each drug concentration repeated in triplicate over a range of half-log steps.

- Incubation of cells and drugs is for 36 hrs at 37° under CO₂. At
- 5 the end of the incubation period, cells are examined microscopically for evidence of cell distress. Next, 100 μ l of media containing the secreted alkaline phosphatase is removed from each well and transferred to a microtube array for heat treatment at 65°C for 1 hr to inactivate endogenous alkaline phosphatases (but not the heat stable secreted phosphatase).
- 10 The heat treated media is assayed for alkaline phosphatase by a luminescence assay using the luminescence reagent CSPD® (Tropix, Bedford, Mass.). A volume of 50 μ l media is combined with 200 μ l of CSPD cocktail and incubated for 60 minutes at room temperature. Luminescence is monitored using an ML2200 microplate luminometer (Dynatech). Luminescence reflects the level of
- 15 activation of the fos reporter construct stimulated by the transiently expressed protein.

DNA-CaPO₄ precipitate for 10cm. plate of cells

| | | |
|----|--|-------------|
| | Ras expression plasmid (1 μ g/ μ l) | 10 μ l |
| | DSE-SEAP Plasmid (1 μ g/ μ l) | 2 μ l |
| 20 | Sheared Calf Thymus DNA (1 μ g/ μ l) | 8 μ l |
| | 2M CaCl ₂ | 74 μ l |
| | dH ₂ O | 506 μ l |

2X HBS Buffer

| | |
|----|--|
| 25 | 280mM NaCl |
| | 10mM KCl |
| | 1.5mM Na ₂ HPO ₄ 2H ₂ O |
| | 12mM dextrose |
| | 50mM HEPES |
| 30 | Final pH = 7.05 |

Luminescence Buffer (26ml)

| | | |
|----|---------------------------|-------|
| | Assay Buffer | 20ml |
| | Emerald Reagent™ (Tropix) | 2.5ml |
| 35 | 100mM homoarginine | 2.5ml |

CSPD Reagent® (Tropix) 1.0ml

Assay Buffer

Add 0.05M Na₂CO₃ to 0.05M NaHCO₃ to obtain pH 9.5.

5 Make 1mM in MgCl₂

EXAMPLE 182

10 The processing assays employed are modifications of that described by DeClue et al [Cancer Research 51, 712-717, 1991].

K4B-Ras processing inhibition assay

PSN-1 (human pancreatic carcinoma) or viral-K4B-ras-transformed Rat1 cells are used for analysis of protein processing. Subconfluent cells in 100 mm
15 dishes are fed with 3.5 ml of media (methionine-free RPMI supplemented with 2% fetal bovine serum or cysteine-free/methionine-free DMEM supplemented with 0.035 ml of 200 mM glutamine (Gibco), 2% fetal bovine serum, respectively) containing the desired concentration of test compound, lovastatin or solvent alone. Cells treated with lovastatin (5-10 μM), a compound that blocks Ras processing in cells by inhibit-
20 ing a rate-limiting step in the isoprenoid biosynthetic pathway, serve as a positive control. Test compounds are prepared as 1000x concentrated solutions in DMSO to yield a final solvent concentration of 0.1%. Following incubation at 37°C for two hours 204 μCi/ml [³⁵S]Pro-Mix (Amersham, cell labeling grade) is added.

After introducing the label amino acid mixture, the cells are incubated
25 at 37°C for an additional period of time (typically 6 to 24 hours). The media is then removed and the cells are washed once with cold PBS. The cells are scraped into 1 ml of cold PBS, collected by centrifugation (10,000 x g for 10 sec at room temperature), and lysed by vortexing in 1 ml of lysis buffer (1% Nonidet P-40, 20 mM HEPES, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.5% deoxycholate, 0.1% SDS, 1
30 mM DTT, 10 μg/ml AEBSF, 10 μg/ml aprotinin, 2 μg/ml leupeptin and 2 μg/ml antipain). The lysate is then centrifuged at 15,000 x g for 10 min at 4°C and the supernatant saved.

For immunoprecipitation of Ki4B-Ras, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined
35 by the bradford method utilizing bovine serum albumin as a standard. The appropri-

ate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 8 µg of the pan Ras monoclonal antibody, Y13-259, added. The protein/antibody mixture is incubated on ice at 4°C for 24 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 µl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer (0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 µg Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Ras visualized by fluorography.

hDJ Processing Inhibition Assay

PSN-1 cells are seeded in 24-well assay plates. For each compound to be tested, the cells are treated with a minimum of seven concentrations in half-log steps. The final solvent (DMSO) concentration is 0.1%. A vehicle-only control is included on each assay plate. The cells are treated for 24 hours at 37°C / 5% CO₂.

The growth media is then aspirated and the samples are washed with PBS. The cells are lysed with SDS-PAGE sample buffer containing 5% 2-mercaptoethanol and heated to 95°C for 5 minutes. After cooling on ice for 10 minutes, a mixture of nucleases is added to reduce viscosity of the samples.

The plates are incubated on ice for another 10 minutes. The samples are loaded onto pre-cast 8% acrylamide gels and electrophoresed at 15 mA/gel for 3-4 hours. The samples are then transferred from the gels to PVDF membranes by Western blotting.

The membranes are blocked for at least 1 hour in buffer containing 2% nonfat dry milk. The membranes are then treated with a monoclonal antibody to hDJ-2 (Neomarkers Cat. # MS-225), washed, and treated with an alkaline phosphatase-conjugated secondary antibody. The membranes are then treated
5 with a fluorescent detection reagent and scanned on a phosphorimager.

For each sample, the percent of total signal corresponding to the unprenylated species of hDJ (the slower-migrating species) is calculated by densitometry. Dose-response curves and EC₅₀ values are generated using 4-parameter curve fits in SigmaPlot software.

10

EXAMPLE 183

Rap1 processing inhibition assay

15 Protocol A:

Cells are labeled, incubated and lysed as described in Example 182.

For immunoprecipitation of Rap1, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 2 µg of
20 the Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech), is added. The protein/antibody mixture is incubated on ice at 4°C for 1 hour. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and
25 resuspended in 100 µl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer (0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 mg Rap1 antibody,
30 Rap1/Krev1 (121) (Santa Cruz Biotech). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Rap1 is eluted from the beads by heating at 95°C for 5 minutes,

after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Rap1 visualized by fluorography.

5 Protocol B:

PSN-1 cells are passaged every 3-4 days in 10 cm plates, splitting near-confluent plates 1:20 and 1:40. The day before the assay is set up, 5×10^6 cells are plated on 15 cm plates to ensure the same stage of confluency in each assay. The media for these cells is RPMI 1640 (Gibco), with 15% fetal bovine serum and 1x
10 Pen/Strep antibiotic mix.

The day of the assay, cells are collected from the 15 cm plates by trypsinization and diluted to 400,000 cells/ml in media. 0.5 ml of these diluted cells are added to each well of 24-well plates, for a final cell number of 200,000 per well. The cells are then grown at 37°C overnight.

15 The compounds to be assayed are diluted in DMSO in 1/2-log dilutions. The range of final concentrations to be assayed is generally 0.1-100 μ M. Four concentrations per compound is typical. The compounds are diluted so that each concentration is 1000x of the final concentration (i.e., for a 10 μ M data point, a 10 mM stock of the compound is needed).

20 2 μ L of each 1000x compound stock is diluted into 1ml media to produce a 2X stock of compound. A vehicle control solution (2 μ L DMSO to 1ml media), is utilized. 0.5 ml of the 2X stocks of compound are added to the cells.

After 24 hours, the media is aspirated from the assay plates. Each well is rinsed with 1 ml PBS, and the PBS is aspirated. 180 μ L SDS-PAGE sample
25 buffer (Novex) containing 5% 2-mercaptoethanol is added to each well. The plates are heated to 100°C for 5 minutes using a heat block containing an adapter for assay plates. The plates are placed on ice. After 10 minutes, 20 μ L of an RNase/DNase mix is added per well. This mix is 1mg/ml DNaseI (Worthington Enzymes), 0.25 mg/ml Rnase A (Worthington Enzymes), 0.5M Tris-HCl pH8.0 and 50 mM $MgCl_2$.
30 The plate is left on ice for 10 minutes. Samples are then either loaded on the gel, or stored at -70°C until use.

Each assay plate (usually 3 compounds, each in 4-point titrations, plus controls) requires one 15-well 14% Novex gel. 25 μ l of each sample is loaded onto the gel. The gel is run at 15mA for about 3.5 hours. It is important to run the gel far

enough so that there will be adequate separation between 21kd (Rap1) and 29kd (Rab6).

5 The gels are then transferred to Novex pre-cut PVDF membranes for 1.5 hours at 30V (constant voltage). Immediately after transferring, the membranes are blocked overnight in 20ml Western blocking buffer (2% nonfat dry milk in Western wash buffer (PBS + 0.1% Tween-20). If blocked over the weekend, 0.02% sodium azide is added. The membranes are blocked at 4°C with slow rocking.

10 The blocking solution is discarded and 20ml fresh blocking solution containing the anti Rap1a antibody (Santa Cruz Biochemical SC1482) at 1:1000 (diluted in Western blocking buffer) and the anti Rab6 antibody (Santa Cruz Biochemical SC310) at 1:5000 (diluted in Western blocking buffer) are added. The membranes are incubated at room temperature for 1 hour with mild rocking. The blocking solution is then discarded and the membrane is washed 3 times with Western wash buffer for 15 minutes per wash. 20 ml blocking solution containing 1:1000
15 (diluted in Western blocking buffer) each of two alkaline phosphatase conjugated antibodies (Alkaline phosphatase conjugated Anti-goat IgG and Alkaline phosphatase conjugated anti-rabbit IgG [Santa Cruz Biochemical]) is then added. The membrane is incubated for one hour and washed 3x as above.

20 About 2 ml per gel of the Amersham ECF detection reagent is placed on an overhead transparency (ECF) and the PVDF membranes are placed face down onto the detection reagent. This is incubated for one minute, then the membrane is placed onto a fresh transparency sheet.

25 The developed transparency sheet is scanned on a phosphorimager and the Rap1a Minimum Inhibitory Concentration is determined from the lowest concentration of compound that produces a detectable Rap1a Western signal. The Rap1a antibody used recognizes only unprenylated/unprocessed Rap1a, so that the presence of a detectable Rap1a Western signal is indicative of inhibition of Rap1a prenylation.

30 Protocol C:

This protocol allows the determination of an EC₅₀ for inhibition of processing of Rap1a. The assay is run as described in Protocol B with the following modifications. 20 µl of sample is run on pre-cast 10-20% gradient acrylamide mini gels (Novex Inc.) at 15 mA/gel for 2.5-3 hours. Prenylated and
35 unprenylated forms of Rap1a are detected by blotting with a polyclonal antibody

- (Rap1/Krev-1 Ab#121; Santa Cruz Research Products #sc-65), followed by an alkaline phosphatase-conjugated anti-rabbit IgG antibody. The percentage of unprenylated Rap1a relative to the total amount of Rap1a is determined by peak integration using Imagequant[™] software (Molecular Dynamics). Unprenylated
- 5 Rap1a is distinguished from prenylated protein by virtue of the greater apparent molecular weight of the prenylated protein. Dose-response curves and EC₅₀ values are generated using 4-parameter curve fits in SigmaPlot software.

EXAMPLE 184

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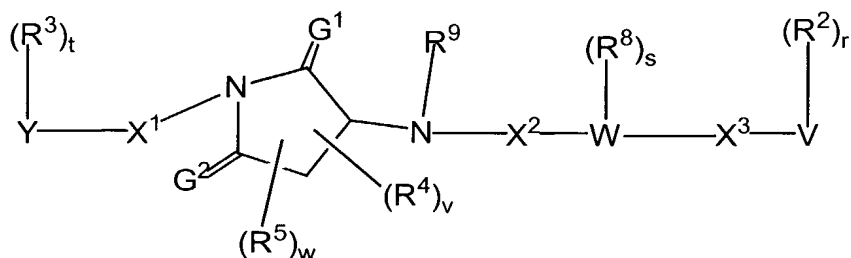
In vivo tumor growth inhibition assay (nude mouse)

- In vivo* efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art. Examples of such *in vivo* efficacy studies are described by N. E. Kohl et al. (Nature Medicine, 1:792-797
- 15 (1995)) and N. E. Kohl et al. (Proc. Nat. Acad. Sci. U.S.A., 91:9141-9145 (1994)).

- Rodent fibroblasts transformed with oncogenically mutated human Ha-ras or Ki-ras (10⁶ cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination
- 20 treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of
- 25 0.5-1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1. A compound of the formula A:



A

5 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

X^2 is $(C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_p$;

10

X^3 is $(C(R^{1c})_2)_q A^4 (C(R^{1c})_2)_q$;

R^{1a} , R^{1b} and R^{1c} are independently selected from:

- 15 a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and
- 20 $R^{10}OC(O)NR^{10}$ -, and
- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6
- 25 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$,

-C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

A¹, A³ and A⁴ are independently selected from

- 5 a) a bond,
- b) -C(=O)-,
- c) -HC=CH-,
- d) -C≡C-,
- e) O,
- 10 f) NR¹⁰,
- g) NR¹⁰C(O),
- h) C(O)NR¹⁰,
- i) OC(O)NR¹⁰,
- j) NR¹⁰C(O)O,
- 15 k) S(=O)_m,
- l) C(O)O, and
- m) OC(O);

A² is selected from

- 20 a) a bond,
- b) -C(=O)-,
- c) NR¹⁰C(O),
- d) S(=O)_m, and
- e) OC(O);

25

R² is independently selected from:

- a) hydrogen,
- b) CN,
- c) NO₂,
- 30 d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- g) C₁-C₆ alkyl, unsubstituted or substituted,
- h) OR¹⁰,

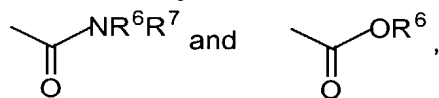
- i) N_3 ,
 j) $R^{6a}S(O)_m$,
 k) C_3-C_{10} cycloalkyl, unsubstituted or substituted,
 l) C_2-C_6 alkenyl, unsubstituted or substituted,
 5 m) C_2-C_6 alkynyl, unsubstituted or substituted,
 n) $(R^{10})_2NC(O)NR^{10}-$,
 o) $R^{10}C(O)-$,
 p) $R^{10}C(O)NR^{10}-$,
 q) $R^{10}OC(O)-$,
 10 r) $-N(R^{10})_2$,
 s) $R^{10}OC(O)NR^{10}-$, and
 t) $-(C_1-C_6 \text{ alkyl})NR^{10}C(O)R^{13}$;

R^3 is independently selected from:

- 15 H, CN, NO_2 , halo, unsubstituted or substituted C_1-C_6 alkyl, N_3 , oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C_2-C_6 alkenyl, unsubstituted or substituted C_2-C_6
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclylalkyl, C_1-C_6 perfluoroalkyl, CF_3O- , CF_3CH_2- , unsubstituted or
 20 substituted C_3-C_{10} cycloalkyl, OR^{10} , NR^6R^7 , OR^6 , $-C(O)R^{10}$, $-O(C_1-C_6$
 alkyl) OR^{10} , $-S(O)_mR^{6a}$, $-OS(O)_mR^{6a}$, $-C(O)NR^6R^7$, $-NHC(O)R^{10}$, $-(C_1-C_6$
 alkyl) OR^{10} , and $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

R^4 and R^5 are independently selected from:

- 25 H, OR^{10} , unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted
 C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or
 substituted aryl, unsubstituted or substituted heterocycle,

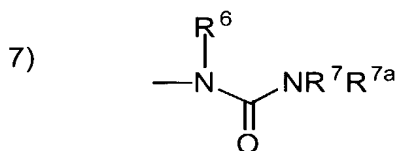
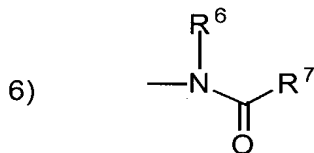


wherein the substituted group is substituted with one or more of:

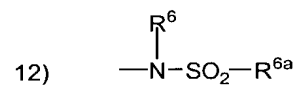
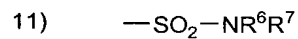
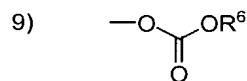
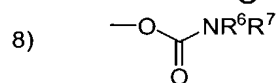
- 30 1) aryl or heterocycle, unsubstituted or substituted with:
 a) C_1-C_6 alkyl,
 b) $(CH_2)_nOR^6$,

5

- c) $(\text{CH}_2)_n \text{NR}^6 \text{R}^7$,
 d) halogen,
 e) CN,
 f) aryl or heteroaryl,
 g) perfluoro- C_1 - C_4 alkyl,
 h) $\text{S}(\text{O})_m \text{R}^{6a}$,

2) C_3 - C_6 cycloalkyl,3) OR^6 ,4) $\text{S}(\text{O})_m \text{R}^{6a}$,5) $-\text{NR}^6 \text{R}^7$,

10



- 15) N_3 ,
- 16) halo, and
- 17) perfluoro- C_{1-4} -alkyl; or

5 R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, $-NC(O)-$, and $-N(COR^{10})-$;


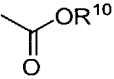
and any of R^4 and R^5 are optionally attached to the same carbon atom;

10

R^6 , R^7 and R^{7a} are independently selected from:

H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

15

- a) C_1-C_6 alkoxy,
- b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- c) halogen,
- d) HO,
- e)  ,
- f)  ,
- g) $-S(O)_m R^{6a}$, or
- h) $N(R^{10})_2$; or

20

R^6 and R^7 may be joined in a ring;

25 R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

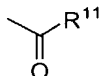
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- 1) C_{1-4} alkoxy,

2) aryl or heterocycle,

3) halogen,

4) HO,

5) ,

5

6) SO₂R^{6a},

7) N(R¹⁰)₆; and

b) C₁-C₆ alkyl, unsubstituted or substituted with one or more of

the following:

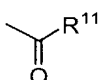
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1) -C(R¹⁰)₂C₁₋₄ alkoxy,

2) aryl or heterocycle,

3) -C(R¹⁰)₂halogen,

4) -C(R¹⁰)₂OH,

5) ,

15

6) -C(R¹⁰)₂SO₂R^{6a}, and

7) -C(R¹⁰)₂N(R¹⁰)₂;

R⁸ is independently selected from

20

a) hydrogen,

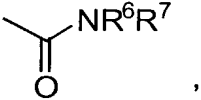
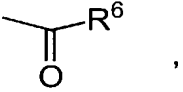
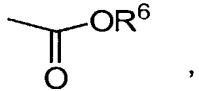
b) unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, unsubstituted or substituted C₃-C₆ cycloalkyl, unsubstituted or substituted C₁-C₄ perfluoroalkyl, F, Cl, Br, R¹⁰O-, CN, R^{6a}S(O)_m-, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, NO₂, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, R¹⁰OC(O)NR¹⁰-, N₃, or -N(R¹⁰)₂, and

25

c) C₁-C₆ alkyl, unsubstituted or substituted by C₁-C₄ perfluoroalkyl, F, Cl, Br, R¹⁰O-, R^{6a}S(O)_m-, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, CN, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, N₃, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

30

R⁹ is independently selected from

- 1) H, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted C₂-C₈ alkenyl, unsubstituted or substituted C₂-C₈ alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- 5 a) C₁-C₆ alkyl, unsubstituted or substituted,
 b) (CH₂)_nOR⁶,
 c) (CH₂)_nNR⁶R⁷,
 d) halogen,
 10 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro-C₁-C₄ alkyl,
 i) S(O)_mR^{6a},
 15 j) N(R¹⁰)₂,
 k) NR¹⁰C(O)R¹¹,
 l) NR¹⁰C(O)R¹¹N(R¹⁰)₂,
 m) -R¹⁰(CH₂)_nR¹¹,
- 2) C₃-C₆ cycloalkyl,
 20 3) S(O)_mR^{6a},
- 4) ,
- 5) $\text{—SO}_2\text{—NR}^6\text{R}^7$,
- 6) ,
- 7) , and
- 8) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³ ;

R¹⁰ is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted C₁-C₆ alkyl,
- c) C₃-C₆ cycloalkyl,
- 5 d) 2,2,2-trifluoroethyl,
- e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

10

R¹¹ is independently selected from

- a) unsubstituted or substituted C₁-C₆ alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- 15 d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclalkyl;

R¹³ is independently selected from

- a) H,
- 20 b) unsubstituted or substituted C₁-C₆ alkyl,
- c) unsubstituted or substituted aryl,
- d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclalkyl, unsubstituted or substituted,
- 25 g) C₂-C₆ alkynyl, unsubstituted or substituted,
- h) C₂-C₆ alkenyl, unsubstituted or substituted,
- i) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
- j) CF₃,
- k) CF₃O-,
- 30 l) CF₃CH₂-,
- m) OR¹⁰,
- n) -C(O)R¹⁰,
- o) -O(C₁-C₆ alkyl)OR¹⁰,
- p) -C(O)NR⁶R⁷,

- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 and G^2 are independently selected from oxygen or H_2 ;

5

V is selected from

- a) hydrogen,
 b) heterocycle,
 c) aryl,
 10 d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a
 heteroatom selected from O, $S(O)_m$, and N, and
 e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^4 is $S(O)_m$ and q is 0;

15 W is a heterocycle;

Y is selected from

- a) H,
 b) C_1-C_8 alkyl,
 20 c) C_2-C_8 alkenyl,
 d) C_2-C_8 alkynyl,
 e) C_3-C_{20} cycloalkyl,
 f) aryl, and
 g) heterocycle;

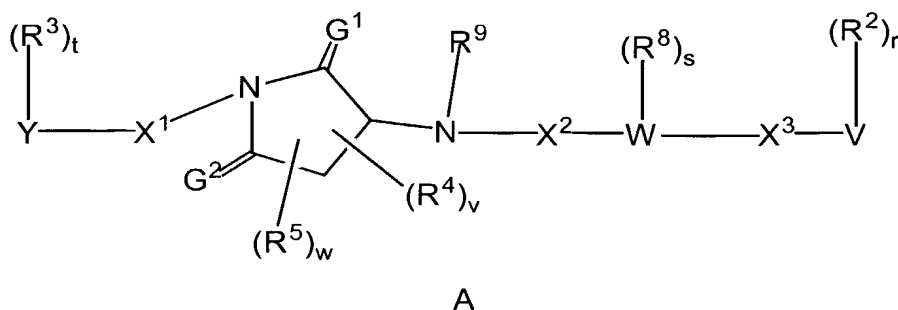
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- m is 0, 1 or 2;
 n is 0, 1, 2, 3, 4, 5 or 6;
 p is 0, 1, 2, 3, 4, 5 or 6;
 q is 0, 1, 2, 3, 4, 5 or 6;
 30 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and

w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

5 2. The compound according to Claim 1 illustrated by formula A:



wherein

X^1 is $(C(R^{1c})_2)_n A^1 (C(R^{1c})_2)_n A^2$;

10

X^2 is $(C(R^{1b})_2)_p A^3 (C(R^{1b})_2)_p$;

X^3 is $(C(R^{1c})_2)_q A^4$;

15 R^{1a} and R^{1b} are independently selected from:

- a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and
- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or

25

substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

5

R^{1c} is selected from

- a) hydrogen and
 - b) unsubstituted or substituted C₁-C₆ alkyl, wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted
- 10 aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, R¹⁰C(O)NR¹⁰-, -C(O)NR⁶R⁷, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

15

A¹ and A³ are independently selected from

- a) a bond,
- b) -C(=O)-,
- c) O,
- 20 d) NR¹⁰,
- e) NR¹⁰C(O),
- f) C(O)NR¹⁰,
- g) OC(O)NR¹⁰,
- h) NR¹⁰C(O)O,
- 25 i) S(=O)_m,
- j) OC(O), and
- k) C(O)O;

A² is selected from

30

- a) a bond,
- b) -C(=O)-,
- c) NR¹⁰C(O), and
- d) S(=O)_m;

A⁴ is a bond;

R² is independently selected from:

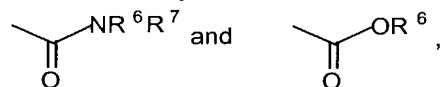
- a) hydrogen,
- 5 b) CN,
- c) NO₂,
- d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- 10 g) C₁-C₆ alkyl, unsubstituted or substituted,
- h) OR¹⁰,
- i) N₃,
- j) R^{6a}S(O)_m,
- k) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
- 15 l) C₂-C₆ alkenyl, unsubstituted or substituted,
- m) C₂-C₆ alkynyl, unsubstituted or substituted,
- n) (R¹⁰)₂NC(O)NR¹⁰-,
- o) R¹⁰C(O)-,
- p) R¹⁰C(O)NR¹⁰-,
- 20 q) R¹⁰OC(O)-,
- r) -N(R¹⁰)₂,
- s) R¹⁰OC(O)NR¹⁰-, and
- t) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³;

25 R³ is independently selected from:

- H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 30 heterocyclalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -OS(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆
 alkyl)OR¹⁰, and -(C₁-C₆ alkyl)C(O)R¹⁰;

R^4 and R^5 are independently selected from:

H, OR^{10} , unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_2 - C_8 alkenyl, unsubstituted or substituted C_2 - C_8 alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

a) C_1 - C_6 alkyl,

b) $(CH_2)_nOR^6$,

10 c) $(CH_2)_nNR^6R^7$,

d) halogen,

e) CN,

f) aryl or heteroaryl,

g) perfluoro- C_1 - C_4 alkyl,

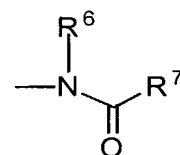
15 h) $S(O)_mR^{6a}$,

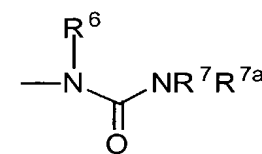
2) C_3 - C_6 cycloalkyl,

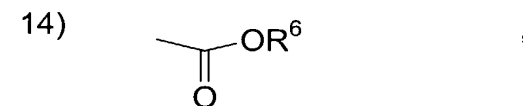
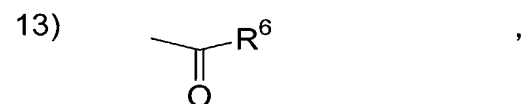
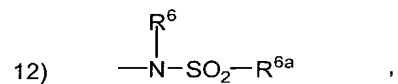
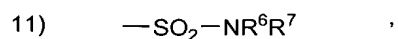
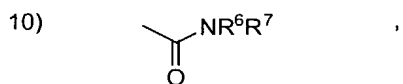
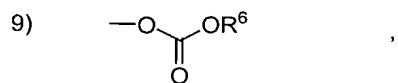
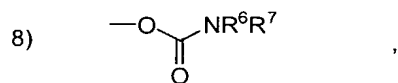
3) OR^6 ,

4) $S(O)_mR^{6a}$,

5) $-NR^6R^7$,

6)  ,

7)  ,



15) N_3 ,

16) halo, and

17) perfluoro- C_{1-4} -alkyl; or

R^4 and R^5 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$

wherein one of the carbon atoms is optionally replaced by a moiety selected from:

10 O, S(O)_m , NR^{10} , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

15 H, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, $\text{C}_1\text{—C}_4$ perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

a) $\text{C}_1\text{—C}_6$ alkoxy,

b) substituted or unsubstituted aryl or substituted or
20 unsubstituted heterocycle,

c) halogen,

- d) HO,
- e) $\text{C}(=\text{O})\text{R}^{11}$, ,
- f) $\text{C}(=\text{O})\text{OR}^{10}$, ,
- g) $-\text{S}(\text{O})_m\text{R}^{6a}$, or
- h) $\text{N}(\text{R}^{10})_2$; or

5 R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

10 a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 15 4) HO,

- 5) $\text{C}(=\text{O})\text{R}^{11}$, ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

20 b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of the following:

- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 25 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) $\text{C}(=\text{O})\text{R}^{11}$, ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

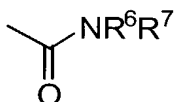
- a) hydrogen,
- b) unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, unsubstituted or substituted C_3 - C_6 cycloalkyl, unsubstituted or substituted C_1 - C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O$ -, CN, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, NO_2 , $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, $R^{10}OC(O)NR^{10}$ -, N_3 , or $-N(R^{10})_2$, and
- c) C_1 - C_6 alkyl, unsubstituted or substituted by C_1 - C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O$ -, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, CN, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, N_3 , $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^9 is independently selected from

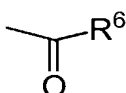
- 1) H, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_2 - C_8 alkenyl, unsubstituted or substituted C_2 - C_8 alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
 - a) C_1 - C_6 alkyl, unsubstituted or substituted,
 - b) $(CH_2)_nOR^6$,
 - c) $(CH_2)_nNR^6R^7$,
 - d) halogen,
 - e) CN,
 - f) aryl, unsubstituted or substituted,
 - g) heterocycle, unsubstituted or substituted,
 - h) perfluoro- C_1 - C_4 alkyl,
 - i) $S(O)_mR^{6a}$,
 - j) $N(R^{10})_2$,
 - k) $NR^{10}C(O)R^{11}$,
 - l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 - m) $-R^{10}(CH_2)_nR^{11}$,

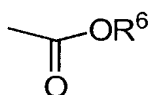
2) C_3-C_6 cycloalkyl,

3) $S(O)_m R^{6a}$,

4) ,

5) $-SO_2-NR^6R^7$,

6) ,

7) , and

8) $-(C_1-C_6 \text{ alkyl})NR^{10}C(O)R^{13}$;

R^{10} is independently selected from

- a) hydrogen,
- 10 b) unsubstituted or substituted C_1-C_6 alkyl,
- c) C_3-C_6 cycloalkyl,
- d) 2,2,2-trifluoroethyl,
- e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- 15 g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

R^{11} is independently selected from

- a) unsubstituted or substituted C_1-C_6 alkyl,
- 20 b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted C_1 - C_6 alkyl,
- c) unsubstituted or substituted aryl,
- 5 d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclylalkyl, unsubstituted or substituted,
- g) C_2 - C_6 alkynyl, unsubstituted or substituted,
- h) C_2 - C_6 alkenyl, unsubstituted or substituted,
- 10 i) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
- j) CF_3 ,
- k) CF_3O -,
- l) CF_3CH_2 -,
- m) OR^{10} ,
- 15 n) $-C(O)R^{10}$,
- o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
- p) $-C(O)NR^6R^7$,
- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
- r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

20

G^1 and G^2 are independently selected from oxygen or H_2 ;

V is selected from

- a) heterocycle,
- 25 b) aryl, and
- c) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, $S(O)_m$, and N, and

W is a heterocycle;

30

Y is selected from

- a) H,
- b) C_1 - C_8 alkyl,
- c) C_3 - C_{20} cycloalkyl,

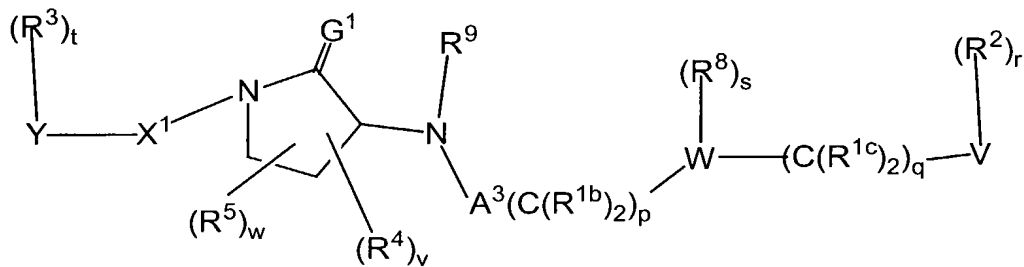
- d) aryl, or
e) heterocycle;

- m is 0, 1 or 2;
5 n is 0, 1, 2, 3, 4, 5 or 6;
p is 0, 1, 2, 3, 4, 5 or 6;
q is 0, 1, 2, or 3;
r is 0 to 5;
s is 0, 1, 2, 3 or 4;
10 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
u is 4 or 5;
v is 0, 1, 2, 3 or 4; and
w is 0, 1, 2, 3 or 4;

- 15 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

3. The compound according to Claim 1, as illustrated by formula

B:



B

- 20 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- 25 a) hydrogen;

- 5 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀ cycloalkyl, R¹⁰O-, R^{6a}S(O)_m, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, -C(O)NR⁶R⁷, R¹⁰C(O)NR¹⁰-, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, -N(R¹⁰)₂, R¹⁰OC(O)-, and R¹⁰OC(O)NR¹⁰-, and
- 10 c) unsubstituted or substituted C₁-C₆ alkyl, wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, R¹⁰C(O)NR¹⁰-, -C(O)NR⁶R⁷, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;

R^{1b} and R^{1c} are independently selected from

- 15 a) hydrogen and
- b) unsubstituted or substituted C₁-C₆ alkyl, wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C₃-C₁₀cycloalkyl, unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆ alkynyl, R¹⁰O-, R^{6a}S(O)_m, R¹⁰C(O)NR¹⁰-, -C(O)NR⁶R⁷, (R¹⁰)₂NC(O)NR¹⁰-, R¹⁰C(O)-, R¹⁰OC(O)-, halo, -N(R¹⁰)₂, and R¹⁰OC(O)NR¹⁰-;
- 20

A¹ is selected from

- 25 a) a bond,
- b) -C(=O)-,
- c) O,
- d) NR¹⁰,
- e) NR¹⁰C(O),
- 30 f) C(O)NR¹⁰,
- g) OC(O)NR¹⁰,
- h) NR¹⁰C(O)O,
- i) S(=O)_m,
- j) C(O)O, and

k) OC(O) ;

A^2 is selected from

- 5 a) a bond,
 b) $-\text{C(=O)}-$,
 c) $\text{NR}^{10}\text{C(O)}$, and
 d) S(=O)_m ;

A^3 is selected from a bond or C(=O) ;

10

R^2 is independently selected from:

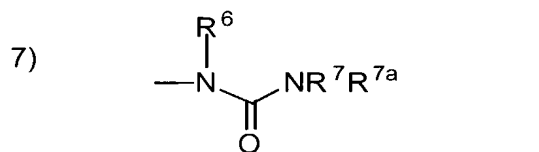
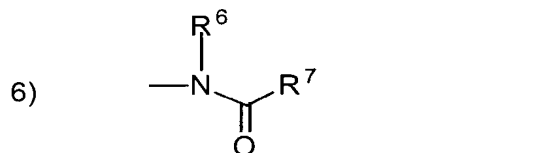
- a) hydrogen,
 b) CN ,
 c) NO_2 ,
 15 d) halogen,
 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
 h) OR^{10} ,
 20 i) N_3 ,
 j) $\text{R}^{6a}\text{S(O)}_m$,
 k) $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted,
 l) $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted,
 m) $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted,
 25 n) $(\text{R}^{10})_2\text{NC(O)NR}^{10}-$,
 o) $\text{R}^{10}\text{C(O)}-$,
 p) $\text{R}^{10}\text{C(O)NR}^{10}-$,
 q) $\text{R}^{10}\text{OC(O)}-$,
 r) $-\text{N(R}^{10})_2$,
 30 s) $\text{R}^{10}\text{OC(O)NR}^{10}-$, and
 t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C(O)R}^{13}$;

R^3 is independently selected from:

H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰,
 and -(C₁-C₆ alkyl)C(O)R¹⁰;

10 R⁴ and R⁵ are independently selected from:
 H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted
 aryl, unsubstituted or substituted heterocycle, wherein the substituted group is
 substituted with one or more of:

- 15 1) aryl or heterocycle, unsubstituted or substituted with:
 a) C₁-C₆ alkyl,
 b) (CH₂)_nOR⁶,
 c) (CH₂)_nNR⁶R⁷,
 d) halogen,
 e) CN,
 20 f) aryl or heteroaryl,
 g) perfluoro-C₁-C₄ alkyl,
 h) S(O)_mR^{6a},
 2) C₃-C₆ cycloalkyl,
 3) OR⁶,
 25 4) S(O)_mR^{6a},
 5) —NR⁶R⁷,



- 8) $\text{—O—C(=O)—NR}^6\text{R}^7$,
- 9) —O—C(=O)—OR^6 ,
- 10) $\text{—C(=O)—NR}^6\text{R}^7$,
- 11) $\text{—SO}_2\text{—NR}^6\text{R}^7$,
- 12) $\begin{array}{c} \text{R}^6 \\ | \\ \text{—N—SO}_2\text{—R}^{6a} \end{array}$,
- 13) —C(=O)—R^6 ,
- 14) —C(=O)—OR^6 ,
- 15) N_3 ,
- 16) halo, and
- 17) perfluoro- C_{1-4} -alkyl; or

5

R^4 and R^5 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$ wherein one of the carbon atoms is optionally replaced by a moiety selected from:

10 O, S(O)_m , NR^{10} , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

and any of R^4 and R^5 are optionally attached to the same carbon atom;


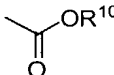
15 R^6 , R^7 and R^{7a} are independently selected from:

H, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, $\text{C}_1\text{—C}_4$ perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

a) $\text{C}_1\text{—C}_6$ alkoxy,

b) substituted or unsubstituted aryl or substituted or

20 unsubstituted heterocycle,

- c) halogen,
- d) HO,
- e) ,
- f) ,
- g) $-\text{S}(\text{O})_m\text{R}^{6a}$, or
- h) $\text{N}(\text{R}^{10})_2$; or

5

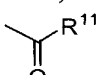
R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

10 R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

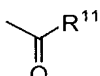
15

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) HO,
- 5) ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

20

b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of the following:

25

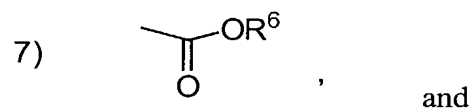
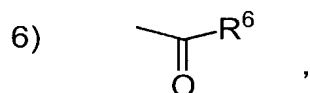
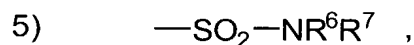
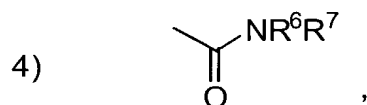
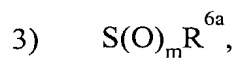
- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

- 5 a) hydrogen,
 b) unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted
 C_2 - C_6 alkynyl, unsubstituted or substituted C_3 - C_6 cycloalkyl,
 unsubstituted or substituted C_1 - C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O$ -,
 CN, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, NO_2 , $(R^{10})_2NC(O)NR^{10}$ -,
 $R^{10}C(O)$ -, $R^{10}OC(O)$ -, $R^{10}OC(O)NR^{10}$ -, N_3 , or $-N(R^{10})_2$, and
 c) C_1 - C_6 alkyl, unsubstituted or substituted by C_1 - C_4 perfluoroalkyl,
 F, Cl, Br, $R^{10}O$ -, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, CN,
 $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, N_3 , $-N(R^{10})_2$, and
 $R^{10}OC(O)NR^{10}$ -;
- 10

R^9 is independently selected from

- 15 1) H, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or
 substituted C_2 - C_8 alkenyl, unsubstituted or substituted C_2 - C_8 alkynyl,
 unsubstituted or substituted aryl, and unsubstituted or substituted
 heterocycle, wherein the substituted group is substituted with one or
 more of:
 a) C_1 - C_6 alkyl, unsubstituted or substituted,
 b) $(CH_2)_nOR^6$,
 c) $(CH_2)_nNR^6R^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1 - C_4 alkyl,
 i) $S(O)_mR^{6a}$,
 j) $N(R^{10})_2$,
 k) $NR^{10}C(O)R^{11}$,
 l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 m) $-R^{10}(CH_2)_nR^{11}$,
 2) C_3 - C_6 cycloalkyl,
- 20
- 25
- 30



5

R^{10} is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted C_1-C_6 alkyl,
- c) C_3-C_6 cycloalkyl,
- 10 d) 2,2,2-trifluoroethyl,
- e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

15

R^{11} is independently selected from

- a) unsubstituted or substituted C_1-C_6 alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- 20 d) unsubstituted or substituted aryl, and
- e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,

- b) unsubstituted or substituted C_1-C_6 alkyl,
 c) unsubstituted or substituted aryl,
 d) unsubstituted or substituted heterocycle,
 e) aralkyl, unsubstituted or substituted,
 5 f) heterocyclylalkyl, unsubstituted or substituted,
 g) C_2-C_6 alkynyl, unsubstituted or substituted,
 h) C_2-C_6 alkenyl, unsubstituted or substituted,
 i) C_3-C_{10} cycloalkyl, unsubstituted or substituted,
 j) CF_3 ,
 10 k) CF_3O- ,
 l) CF_3CH_2- ,
 m) OR^{10} ,
 n) $-C(O)R^{10}$,
 o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
 15 p) $-C(O)NR^6R^7$,
 q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 is selected from oxygen or H_2 ;

20

V is aryl or heteroaryl;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinoliny, isoquinoliny, and thienyl;

25

Y is selected from

- a) H,
 b) C_1-C_8 alkyl,
 c) C_3-C_{20} cycloalkyl,
 30 d) aryl or
 e) heterocycle;

m is 0, 1 or 2;

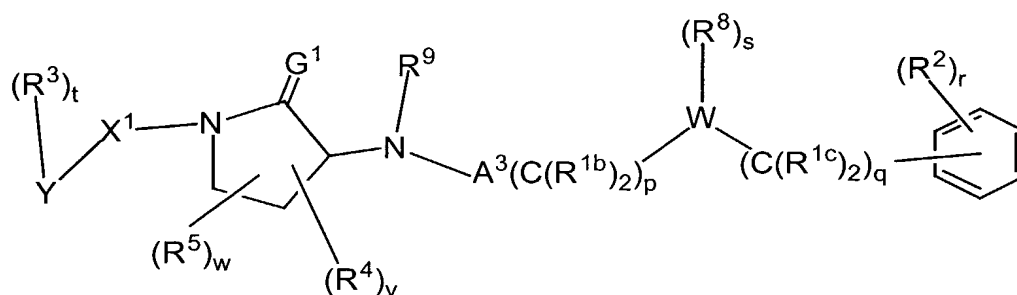
n is 0, 1, 2, 3, 4, 5 or 6;

- p is 0, 1, 2, 3, or 4;
 q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 5 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

10 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

4. The compound according to Claim 1, as illustrated by formula

C:



C

15 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- 20 a) hydrogen;
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$,
 25 $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and

- c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
 b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

A^1 is selected from

- a) a bond,
 b) $-C(=O)$ -,
 c) O,
 d) NR^{10} ,
 e) $NR^{10}C(O)$,
 f) $C(O)NR^{10}$,
 g) $OC(O)NR^{10}$,
 h) $NR^{10}C(O)O$,
 i) $S(=O)_m$,
 j) $C(O)O$, and
 k) $OC(O)$;

A^2 is selected from

- a) a bond,
 b) $-C(=O)$ -,

- c) $\text{NR}^{10}\text{C(O)}$, and
- d) S(=O)_m ;

A^3 is selected from

- 5 a) a bond, or
- b) C(=O) ;

R^2 is independently selected from:

- a) hydrogen,
- 10 b) CN ,
- c) NO_2 ,
- d) halogen,
- e) aryl, unsubstituted or substituted,
- f) heterocycle, unsubstituted or substituted,
- 15 g) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
- h) OR^{10} ,
- i) N_3 ,
- j) $\text{R}^{6a}\text{S(O)}_m$,
- k) $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted,
- 20 l) $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted,
- m) $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted,
- n) $(\text{R}^{10})_2\text{NC(O)NR}^{10}-$,
- o) $\text{R}^{10}\text{C(O)}-$,
- p) $\text{R}^{10}\text{C(O)NR}^{10}-$,
- 25 q) $\text{R}^{10}\text{OC(O)}-$,
- r) $-\text{N(R}^{10})_2$,
- s) $\text{R}^{10}\text{OC(O)NR}^{10}-$, and
- t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C(O)R}^{13}$;

30 R^3 is independently selected from:

H , CN , NO_2 , halo, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, N_3 , oxido, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted

heterocyclalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR⁶R⁷, OR⁶, -C(O)R¹⁰, -O(C₁-C₆ alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR⁶R⁷, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰, and -(C₁-C₆ alkyl)C(O)R¹⁰;

5

R⁴ and R⁵ are independently selected from:

H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:

10

1) aryl or heterocycle, unsubstituted or substituted with:

a) C₁-C₆ alkyl,

b) (CH₂)_nOR⁶,

c) (CH₂)_nNR⁶R⁷,

d) halogen,

15

e) CN,

f) aryl or heteroaryl,

g) perfluoro-C₁-C₄ alkyl,

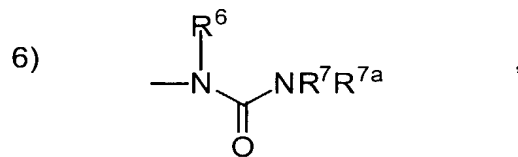
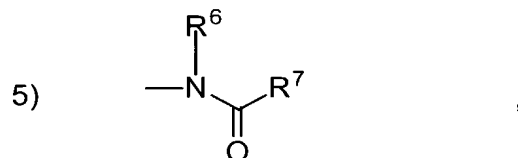
h) S(O)_mR^{6a},

2) C₃-C₆ cycloalkyl,

20

3) OR⁶,

4) —NR⁶R⁷ ,



8) halo, and

9) perfluoro-C₁-4-alkyl; or


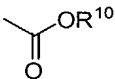
R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, NR^{10} , $-NC(O)-$, and $-N(COR^{10})-$;

5

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

10 H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1-C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

- 15 a) C_1-C_6 alkoxy,
 b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
 c) halogen,
 d) HO,
 e) ,
 f) ,
 g) $-S(O)_mR^{6a}$, or
 h) $N(R^{10})_2$; or

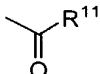
20 R^6 and R^7 may be joined in a ring;

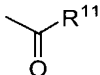
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

25 a) C_3-6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted with one or more of the following:

- 30 1) C_{1-4} alkoxy,
 2) aryl or heterocycle,
 3) halogen,
 4) HO,

- 5)  ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and
- b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of
- the following:

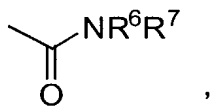
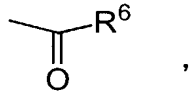
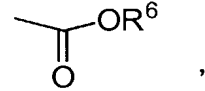
- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5)  ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

R^8 is independently selected from

- a) hydrogen,
- b) F, Cl, Br, $\text{R}^{10}\text{O}-$, CN, $\text{R}^{6a}\text{S}(\text{O})_m-$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, NO_2 , $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$, N_3 , or $-\text{N}(\text{R}^{10})_2$, and
- c) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted by $\text{C}_1\text{-C}_4$ perfluoroalkyl, F, Cl, Br, $\text{R}^{10}\text{O}-$, $\text{R}^{6a}\text{S}(\text{O})_m-$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $\text{R}^{10}\text{C}(\text{O})\text{NR}^{10}-$, CN, $(\text{R}^{10})_2\text{NC}(\text{O})\text{NR}^{10}-$, $\text{R}^{10}\text{C}(\text{O})-$, $\text{R}^{10}\text{OC}(\text{O})-$, N_3 , $-\text{N}(\text{R}^{10})_2$, and $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}-$;

R^9 is independently selected from

- 1) H, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted $\text{C}_2\text{-C}_8$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_8$ alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- a) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
- b) $(\text{CH}_2)_n\text{OR}^6$,

- 5
- c) $(\text{CH}_2)_n \text{NR}^6 \text{R}^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1 - C_4 alkyl,
 i) $\text{S}(\text{O})_m \text{R}^{6a}$,
 j) $\text{N}(\text{R}^{10})_2$,
 k) $\text{NR}^{10} \text{C}(\text{O}) \text{R}^{11}$,
 10 l) $\text{NR}^{10} \text{C}(\text{O}) \text{R}^{11} \text{N}(\text{R}^{10})_2$,
 m) $-\text{R}^{10}(\text{CH}_2)_n \text{R}^{11}$,
 2) C_3 - C_6 cycloalkyl,
 3) $\text{S}(\text{O})_m \text{R}^{6a}$,
 4) ,
 5) $-\text{SO}_2-\text{NR}^6 \text{R}^7$,
 6) ,
 7) , and
 15 8) $-(\text{C}_1\text{-C}_6 \text{ alkyl}) \text{NR}^{10} \text{C}(\text{O}) \text{R}^{13}$;

R^{10} is independently selected from

- 20 a) hydrogen,
 b) unsubstituted or substituted C_1 - C_6 alkyl,
 c) C_3 - C_6 cycloalkyl,
 d) 2,2,2-trifluoroethyl,
 e) unsubstituted or substituted heteroaryl,
 f) unsubstituted or substituted aryl,

- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

R^{11} is independently selected from

- 5 a) unsubstituted or substituted C_1 - C_6 alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted aryl, and
- 10 e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted C_1 - C_6 alkyl,
- c) unsubstituted or substituted aryl,
- 15 d) unsubstituted or substituted heterocycle,
- e) aralkyl, unsubstituted or substituted,
- f) heterocyclalkyl, unsubstituted or substituted,
- g) C_2 - C_6 alkynyl, unsubstituted or substituted,
- h) C_2 - C_6 alkenyl, unsubstituted or substituted,
- 20 i) C_3 - C_{10} cycloalkyl, unsubstituted or substituted,
- j) CF_3 ,
- k) CF_3O -,
- l) CF_3CH_2 -,
- m) OR^{10} ,
- 25 n) $-C(O)R^{10}$,
- o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
- p) $-C(O)NR^6R^7$,
- q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
- 30 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 is selected from oxygen or H_2 ;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl;

Y is selected from

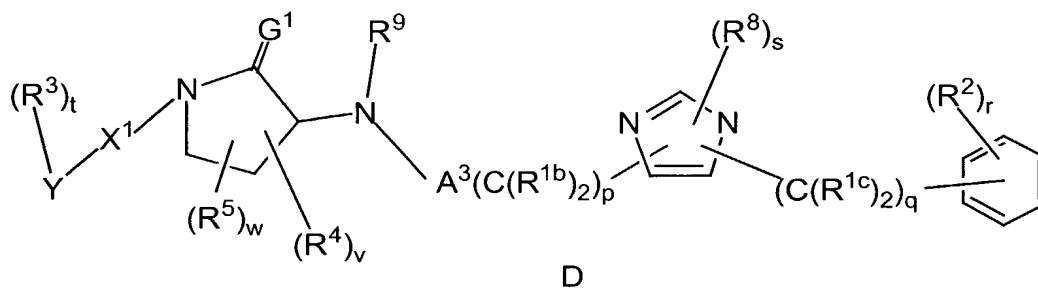
- 5 a) H,
 b) C₁-C₈ alkyl,
 c) C₃-C₂₀ cycloalkyl,
 d) aryl, or
 e) heterocycle;

- m is 0, 1 or 2;
 10 n is 0, 1, 2, 3, 4, 5 or 6;
 p is 0, 1, 2, 3, or 4;
 q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 15 t is 0, 1, 2, 3 or 4; provided that t is 0 when Y is hydrogen;
 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

- 20 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

5. The compound according to Claim 1, as illustrated by formula

D:



- 25 wherein

X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- a) hydrogen;
- b) 5 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -, $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)(NR^{10})$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -; and
- c) 10 unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, 15 $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
- b) 20 unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, 25 $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)(NR^{10})$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

A^1 is selected from

- a) a bond,
- b) 30 $-C(=O)$ -,
- c) O,
- d) NR^{10} ,
- e) $NR^{10}C(O)$,
- f) $C(O)NR^{10}$,

- g) OC(O)NR^{10} ,
 h) $\text{NR}^{10}\text{C(O)O}$,
 i) S(=O)_m ,
 j) C(O)O , and
 5 k) OC(O) ;

A^2 is selected from

- a) a bond,
 b) $-\text{C(=O)}-$,
 10 c) $\text{NR}^{10}\text{C(O)}$, and
 d) S(=O)_m ;

A^3 is selected from

- a) a bond or
 15 b) C(=O) ;

R^2 is independently selected from:

- a) hydrogen,
 b) CN ,
 20 c) NO_2 ,
 d) halogen,
 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted,
 25 h) OR^{10} ,
 i) N_3 ,
 j) $\text{R}^{6a}\text{S(O)}_m$,
 k) $\text{C}_3\text{-C}_{10}$ cycloalkyl, unsubstituted or substituted,
 l) $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted,
 30 m) $\text{C}_2\text{-C}_6$ alkynyl, unsubstituted or substituted,
 n) $(\text{R}^{10})_2\text{NC(O)NR}^{10}-$,
 o) $\text{R}^{10}\text{C(O)}-$,
 p) $\text{R}^{10}\text{C(O)NR}^{10}-$,
 q) $\text{R}^{10}\text{OC(O)}-$,

- r) $-\text{N}(\text{R}^{10})_2$,
- s) $\text{R}^{10}\text{OC}(\text{O})\text{NR}^{10}$ -, and
- t) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C}(\text{O})\text{R}^{13}$;

5 R^3 is independently selected from:

H, CN, NO_2 , halo, unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, N_3 , oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 unsubstituted or substituted $\text{C}_2\text{-C}_6$ alkenyl, unsubstituted or substituted $\text{C}_2\text{-C}_6$
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 10 heterocyclylalkyl, $\text{C}_1\text{-C}_6$ perfluoroalkyl, $\text{CF}_3\text{O-}$, $\text{CF}_3\text{CH}_2\text{-}$, unsubstituted or
 substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, OR^{10} , NR^6R^7 , OR^6 , $-\text{C}(\text{O})\text{R}^{10}$, $-\text{O}(\text{C}_1\text{-C}_6 \text{ alkyl})$
 OR^{10} , $-\text{S}(\text{O})_m\text{R}^{6a}$, $-\text{C}(\text{O})\text{NR}^6\text{R}^7$, $-\text{NHC}(\text{O})\text{R}^{10}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{OR}^{10}$, and $-(\text{C}_1\text{-C}_6$
 $\text{alkyl})\text{C}(\text{O})\text{R}^{10}$;

15 R^4 and R^5 are independently selected from:

H, OR^{10} , unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl, wherein the substituted
 group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with:
 - a) $\text{C}_1\text{-C}_6$ alkyl,
 - 20 b) $(\text{CH}_2)_n\text{OR}^6$,
 - c) $(\text{CH}_2)_n\text{NR}^6\text{R}^7$,
 - d) halogen,
 - e) CN,
 - f) aryl or heteroaryl,
 - 25 g) perfluoro- $\text{C}_1\text{-C}_4$ alkyl,
 - h) $\text{S}(\text{O})_m\text{R}^{6a}$,
- 2) $\text{C}_3\text{-C}_6$ cycloalkyl,
- 3) OR^6 ,

- 4) $\text{—NR}^6\text{R}^7$,
- 5) $\text{—N}(\text{R}^6)\text{C}(=\text{O})\text{R}^7$,
- 6) $\text{—N}(\text{R}^6)\text{C}(=\text{O})\text{NR}^7\text{R}^{7a}$,
- 7) $\text{—C}(=\text{O})\text{R}^6$,
- 8) halo, and
- 9) perfluoro- C_{1-4} -alkyl; or

5

R^4 and R^5 are attached to the same C atom and are combined to form $\text{—(CH}_2\text{)}_u\text{—}$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, S(O)_m , NR^{10} , —NC(O)— , and $\text{—N(COR}^{10}\text{)—}$;

10

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

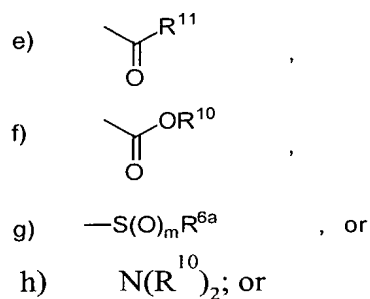
H, $\text{C}_1\text{—C}_6$ alkyl, $\text{C}_3\text{—C}_6$ cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, $\text{C}_1\text{—C}_4$ perfluoroalkyl, unsubstituted or

15

substituted with one or two substituents selected from:

- $\text{C}_1\text{—C}_6$ alkoxy,
- substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- halogen,
- HO,

20



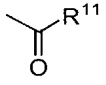
R^6 and R^7 may be joined in a ring;

5

R^7 and R^{7a} may be joined in a ring;

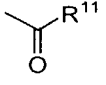
R^{6a} is selected from

a) C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted
 10 with one or more of the following:

- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) HO,
- 5) ,
- 6) SO_2R^{6a} ,
- 7) $\text{N}(\text{R}^{10})_2$; and

15

b) $\text{C}_1\text{-C}_6$ alkyl, unsubstituted or substituted with one or more of
 the following:

- 1) $-\text{C}(\text{R}^{10})_2\text{C}_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-\text{C}(\text{R}^{10})_2$ halogen,
- 4) $-\text{C}(\text{R}^{10})_2\text{OH}$,
- 5) ,
- 6) $-\text{C}(\text{R}^{10})_2\text{SO}_2\text{R}^{6a}$, and
- 7) $-\text{C}(\text{R}^{10})_2\text{N}(\text{R}^{10})_2$;

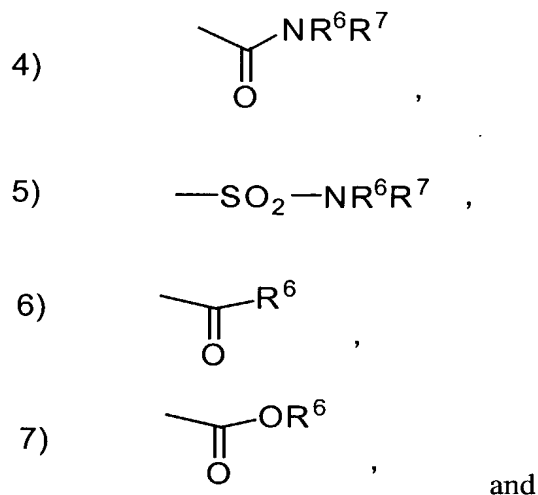
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R^8 is independently selected from

- a) hydrogen, and
 b) C_1-C_6 alkyl, unsubstituted or substituted by C_1-C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O-$, $R^{6a}S(O)_m-$, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}-$, CN, $(R^{10})_2NC(O)NR^{10}-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3 , $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}-$;

R^9 is independently selected from

- 1) H, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted C_2-C_8 alkenyl, unsubstituted or substituted C_2-C_8 alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
- a) C_1-C_6 alkyl, unsubstituted or substituted,
 b) $(CH_2)_nOR^6$,
 c) $(CH_2)_nNR^6R^7$,
 d) halogen,
 e) CN,
 f) aryl, unsubstituted or substituted,
 g) heterocycle, unsubstituted or substituted,
 h) perfluoro- C_1-C_4 alkyl,
 i) $S(O)_mR^{6a}$,
 j) $N(R^{10})_2$,
 k) $NR^{10}C(O)R^{11}$,
 l) $NR^{10}C(O)R^{11}N(R^{10})_2$,
 m) $-R^{10}(CH_2)_nR^{11}$,
- 2) C_3-C_6 cycloalkyl,
 3) $S(O)_mR^{6a}$,



5 R^{10} is independently selected from

- a) hydrogen,
- b) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,
- c) $\text{C}_3\text{—C}_6$ cycloalkyl,
- d) 2,2,2-trifluoroethyl,
- 10 e) unsubstituted or substituted heteroaryl,
- f) unsubstituted or substituted aryl,
- g) unsubstituted or substituted aralkyl, and
- h) unsubstituted or substituted heterocyclalkyl;

15 R^{11} is independently selected from

- a) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,
- b) unsubstituted or substituted aralkyl,
- c) unsubstituted or substituted heterocycle,
- d) unsubstituted or substituted aryl, and
- 20 e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- a) H,
- b) unsubstituted or substituted $\text{C}_1\text{—C}_6$ alkyl,

- 5
- c) unsubstituted or substituted aryl,
 - d) unsubstituted or substituted heterocycle,
 - e) aralkyl, unsubstituted or substituted,
 - f) heterocyclalkyl, unsubstituted or substituted,
 - g) C₂-C₆ alkynyl, unsubstituted or substituted,
 - h) C₂-C₆ alkenyl, unsubstituted or substituted,
 - i) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
 - j) CF₃,
 - k) CF₃O-,
 - 10 l) CF₃CH₂-,
 - m) OR¹⁰,
 - n) -C(O)R¹⁰,
 - o) -O(C₁-C₆ alkyl)OR¹⁰,
 - p) -C(O)NR⁶R⁷,
 - 15 q) -(C₁-C₆ alkyl)OR¹⁰, and
 - r) -(C₁-C₆ alkyl)C(O)R¹⁰;

G¹ is selected from oxygen or H₂;

20 Y is selected from

- a) C₁-C₈ alkyl,
- b) C₃-C₂₀ cycloalkyl,
- c) aryl, or
- d) heterocycle;

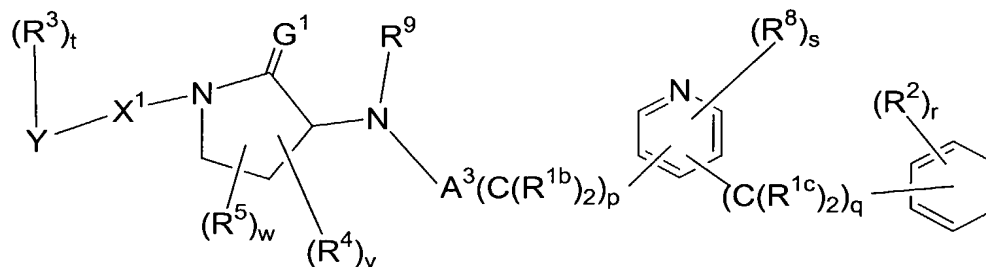
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- m is 0, 1 or 2;
- n is 0, 1, 2, 3, 4, 5 or 6;
- p is 0, 1, 2, 3, or 4;
- q is 0, 1, 2, or 3;
- 30 r is 0 to 5;
- s is 0, 1, 2, 3 or 4;
- t is 0, 1, 2, 3 or 4;
- u is 4 or 5;
- v is 0, 1, 2, 3 or 4; and

w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

- 5 6. The compound according to Claim 1, as illustrated by formula E:



E

wherein

- 10 X^1 is $(C(R^{1a})_2)_n A^1 (C(R^{1a})_2)_n A^2$;

R^{1a} is selected from:

- a) hydrogen;
- b) unsubstituted or substituted aryl, unsubstituted or substituted
 15 heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, $R^{10}O$ -,
 $R^{6a}S(O)_m$, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted
 or substituted C_2 - C_6 alkynyl, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC$
 $(O)(NR^{10})$ -, $R^{10}C(O)$ -, $-N(R^{10})_2$, $R^{10}OC(O)$ -, and $R^{10}OC(O)NR^{10}$ -, and
 c) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the
 20 substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted
 aryl, unsubstituted or substituted heterocycle, unsubstituted or
 substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6
 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$,
 $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -,
 25 , halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

R^{1b} and R^{1c} are independently selected from

- a) hydrogen and
- b) unsubstituted or substituted C_1 - C_6 alkyl, wherein the substituent on the substituted C_1 - C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, unsubstituted or substituted C_3 - C_{10} cycloalkyl, unsubstituted or substituted C_2 - C_6 alkenyl, unsubstituted or substituted C_2 - C_6 alkynyl, $R^{10}O$ -, $R^{6a}S(O)_m$, $R^{10}C(O)NR^{10}$ -, $-C(O)NR^6R^7$, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, halo, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

10

A^1 is selected from

- a) a bond,
- b) $-C(=O)-$,
- c) O,
- 15 d) NR^{10} ,
- e) $NR^{10}C(O)$,
- f) $C(O)NR^{10}$,
- g) $OC(O)NR^{10}$,
- h) $NR^{10}C(O)O$,
- 20 i) $S(=O)_m$,
- j) $C(O)O$, and
- k) $OC(O)$;

25 A^2 is selected from

- a) a bond,
- b) $-C(=O)-$,
- c) $NR^{10}C(O)$, and
- d) $S(=O)_m$;

30 A^3 is selected from

- a) a bond, or
- b) $C(=O)$;

R^2 is independently selected from:

- a) hydrogen,
 b) CN,
 c) NO₂,
 d) halogen,
 5 e) aryl, unsubstituted or substituted,
 f) heterocycle, unsubstituted or substituted,
 g) C₁-C₆ alkyl, unsubstituted or substituted,
 h) OR¹⁰,
 i) N₃,
 10 j) R^{6a}S(O)_m,
 k) C₃-C₁₀ cycloalkyl, unsubstituted or substituted,
 l) C₂-C₆ alkenyl, unsubstituted or substituted,
 m) C₂-C₆ alkynyl, unsubstituted or substituted,
 n) (R¹⁰)₂NC(O)NR¹⁰-,
 15 o) R¹⁰C(O)-,
 p) R¹⁰C(O)NR¹⁰-,
 q) R¹⁰OC(O)-,
 r) -N(R¹⁰)₂,
 s) R¹⁰OC(O)NR¹⁰-, and
 20 t) -(C₁-C₆ alkyl)NR¹⁰C(O)R¹³;

R³ is independently selected from:

- H, CN, NO₂, halo, unsubstituted or substituted C₁-C₆ alkyl, N₃, oxido,
 unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,
 25 unsubstituted or substituted C₂-C₆ alkenyl, unsubstituted or substituted C₂-C₆
 alkynyl, unsubstituted or substituted aralkyl, unsubstituted or substituted
 heterocyclylalkyl, C₁-C₆ perfluoroalkyl, CF₃O-, CF₃CH₂-, unsubstituted or
 substituted C₃-C₁₀ cycloalkyl, OR¹⁰, NR^{6,7}, OR⁶, -C(O)R¹⁰, -O(C₁-C₆
 alkyl)OR¹⁰, -S(O)_mR^{6a}, -C(O)NR^{6,7}, -NHC(O)R¹⁰, -(C₁-C₆ alkyl)OR¹⁰,
 30 and -(C₁-C₆ alkyl)C(O)R¹⁰;

R⁴ and R⁵ are independently selected from:

- H, OR¹⁰, unsubstituted or substituted C₁-C₆ alkyl, wherein the substituted
 group is substituted with one or more of:

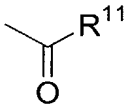
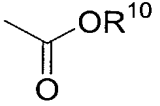
- 1) aryl or heterocycle, unsubstituted or substituted with:
- C_1-C_6 alkyl,
 - $(CH_2)_nOR^6$,
 - $(CH_2)_nNR^6R^7$,
 - halogen,
 - CN,
 - aryl or heteroaryl,
 - perfluoro- C_1-C_4 alkyl,
 - $S(O)_mR^{6a}$,
- 2) C_3-C_6 cycloalkyl,
- 3) OR^6 ,
- 4) $-NR^6R^7$,
- 5) $\begin{array}{c} R^6 \\ | \\ -N-C(=O)R^7 \end{array}$,
- 6) $\begin{array}{c} R^6 \\ | \\ -N-C(=O)NR^7R^{7a} \end{array}$,
- 7) $\begin{array}{c} R^6 \\ | \\ -C(=O)- \end{array}$,
- 8) halo, and
- 9) perfluoro- C_{1-4} -alkyl; or

R^4 and R^5 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, NR^{10} , $-NC(O)-$, and $-N(COR^{10})-$;

and any of R^4 and R^5 are optionally attached to the same carbon atom;

R^6 , R^7 and R^{7a} are independently selected from:

H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, heterocycle, aryl, aralkyl, aroyl, heteraroyl, arylsulfonyl, heteroarylsulfonyl, C_1 - C_4 perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

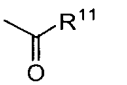
- 5 a) C_1 - C_6 alkoxy,
- b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- c) halogen,
- d) HO,
- e) ,
- f) ,
- 10 g) $-S(O)_m R^{6a}$, or
- h) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;

15

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from

- a) C_3 -6 cycloalkyl, heterocycle, aryl, unsubstituted or substituted
- 20 with one or more of the following:
- 1) C_{1-4} alkoxy,
- 2) aryl or heterocycle,
- 3) halogen,
- 4) HO,
- 5) ,
- 25 6) $SO_2 R^{6a}$,
- 7) $N(R^{10})_2$; and

b) C_1 - C_6 alkyl, unsubstituted or substituted with one or more of the following:

- 1) $-C(R^{10})_2C_{1-4}$ alkoxy,
- 2) aryl or heterocycle,
- 3) $-C(R^{10})_2$ halogen,
- 4) $-C(R^{10})_2OH$,
- 5) $\begin{array}{c} R^{11} \\ \diagup \\ C \\ \parallel \\ O \end{array}$,
- 6) $-C(R^{10})_2SO_2R^{6a}$, and
- 7) $-C(R^{10})_2N(R^{10})_2$;

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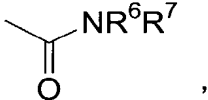
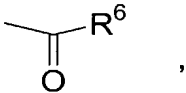
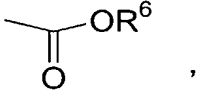
R^8 is independently selected from

- a) hydrogen, and
- b) C_1 - C_6 alkyl, unsubstituted or substituted by C_1 - C_4 perfluoroalkyl, F, Cl, Br, $R^{10}O$ -, $R^{6a}S(O)_m$ -, $-C(O)NR^6R^7$, $R^{10}C(O)NR^{10}$ -, CN, $(R^{10})_2NC(O)NR^{10}$ -, $R^{10}C(O)$ -, $R^{10}OC(O)$ -, N_3 -, $-N(R^{10})_2$, and $R^{10}OC(O)NR^{10}$ -;

15

R^9 is independently selected from

- 1) H, unsubstituted or substituted C_1 - C_6 alkyl, unsubstituted or substituted C_2 - C_8 alkenyl, unsubstituted or substituted C_2 - C_8 alkynyl, unsubstituted or substituted aryl, and unsubstituted or substituted heterocycle, wherein the substituted group is substituted with one or more of:
 - a) C_1 - C_6 alkyl, unsubstituted or substituted,
 - 25 b) $(CH_2)_nOR^6$,
 - c) $(CH_2)_nNR^6R^7$,
 - d) halogen,
 - e) CN,
 - f) aryl, unsubstituted or substituted,
 - 30 g) heterocycle, unsubstituted or substituted,
 - h) perfluoro- C_1 - C_4 alkyl,
 - i) $S(O)_mR^{6a}$,
 - j) $N(R^{10})_2$,

- 5
- k) $\text{NR}^{10}\text{C(O)}\text{R}^{11}$,
 l) $\text{NR}^{10}\text{C(O)}\text{R}^{11}\text{N(R}^{10})_2$,
 m) $-\text{R}^{10}(\text{CH}_2)_n\text{R}^{11}$,
 2) $\text{C}_3\text{-C}_6$ cycloalkyl,
 3) $\text{S(O)}_m\text{R}^{6a}$,
 4) ,
 5) $-\text{SO}_2-\text{NR}^6\text{R}^7$,
 6) ,
 7) , and
 8) $-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{10}\text{C(O)}\text{R}^{13}$;

10 R^{10} is independently selected from

- a) hydrogen,
 b) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
 c) $\text{C}_3\text{-C}_6$ cycloalkyl,
 d) 2,2,2-trifluoroethyl,
 15 e) unsubstituted or substituted heteroaryl,
 f) unsubstituted or substituted aryl,
 g) unsubstituted or substituted aralkyl, and
 h) unsubstituted or substituted heterocyclalkyl;

20 R^{11} is independently selected from

- a) unsubstituted or substituted $\text{C}_1\text{-C}_6$ alkyl,
 b) unsubstituted or substituted aralkyl,
 c) unsubstituted or substituted heterocycle,
 d) unsubstituted or substituted aryl, and

- e) unsubstituted or substituted heterocyclalkyl;

R^{13} is independently selected from

- 5 a) H,
 b) unsubstituted or substituted C_1-C_6 alkyl,
 c) unsubstituted or substituted aryl,
 d) unsubstituted or substituted heterocycle,
 e) aralkyl, unsubstituted or substituted,
 10 f) heterocyclalkyl, unsubstituted or substituted,
 g) C_2-C_6 alkynyl, unsubstituted or substituted,
 h) C_2-C_6 alkenyl, unsubstituted or substituted,
 i) C_3-C_{10} cycloalkyl, unsubstituted or substituted,
 j) CF_3 ,
 15 k) CF_3O- ,
 l) CF_3CH_2- ,
 m) OR^{10} ,
 n) $-C(O)R^{10}$,
 o) $-O(C_1-C_6 \text{ alkyl})OR^{10}$,
 20 p) $-C(O)NR^6R^7$,
 q) $-(C_1-C_6 \text{ alkyl})OR^{10}$, and
 r) $-(C_1-C_6 \text{ alkyl})C(O)R^{10}$;

G^1 is selected from oxygen or H_2 ;

25

Y is selected from

- a) C_1-C_8 alkyl,
 b) C_3-C_{20} cycloalkyl,
 c) aryl, or
 30 d) heterocycle;

m is 0, 1 or 2;

n is 0, 1, 2, 3, 4, 5 or 6;

p is 0, 1, 2, 3, or 4;

- q is 0, 1, 2, or 3;
 r is 0 to 5;
 s is 0, 1, 2, 3 or 4;
 t is 0, 1, 2, 3 or 4;
 5 u is 4 or 5;
 v is 0, 1, 2, 3 or 4; and
 w is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

10

7. A compound which is selected from the group consisting of:

(*R*)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
 benzonitrile,

15

(*S*)-4-{5-[(2-Oxo-1-phenylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
 benzonitrile,

(*R*)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
 benzonitrile,

20

(*S*)-4-{5-[(1-Benzyl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}
 benzonitrile,

(*R*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-
 25 ylmethyl) benzonitrile,

(*S*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-
 ylmethyl)benzonitrile,

30

(*R*)-4-(5-{[1-(3-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-
 ylmethyl)benzonitrile,

(*S*)-4-(5-{[1-(3-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-
 ylmethyl)benzonitrile,

35

(*R*)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

5 (*S*)-4-(5-{[1-(4-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[1-(2-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

10 (*S*)-4-(5-{[1-(2-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

15 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

20 (*R*)-4-(5-{[1-(4-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{[1-(4-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile,

25 (*R*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,

(*S*)-4-{5-[(2-Oxo-1-phenethylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,

30 (*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)acetamide,

35 (*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-(2-oxo-1-phenylpyrrolidin-3-yl)acetamide,

(*R*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]
acetamide,

5 (*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]
acetamide,

(*R*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-
methylacetamide,

10

(*S*)-*N*-(1-Benzyl-2-oxopyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-
methylacetamide,

(*R*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

15

(*S*)-4-{5-[(1-Benzylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,

(*R*)-4-(5-{[Benzyl(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-
ylmethyl)benzonitrile,

20

(*S*)-4-(5-{[Benzyl(1-benzyl-2-oxopyrrolidin-3-yl)amino]methyl}imidazol-1-
ylmethyl)benzonitrile,

(*R*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)phenethylamino]methyl}imidazol-1-
ylmethyl)benzonitrile,

25

(*S*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)phenethylamino]methyl}imidazol-1-
ylmethyl)benzonitrile,

30 (*R*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)(3-phenylpropyl)amino]methyl}imidazol-
1-ylmethyl)benzonitrile,

(*S*)-4-(5-{[(1-Benzyl-2-oxopyrrolidin-3-yl)(3-phenylpropyl)amino]methyl}imidazol-
1-ylmethyl)benzonitrile,

35

(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)(4-phenylbutyl)amino}methyl}imidazol-1-ylmethyl)benzonitrile,

5 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)(4-phenylbutyl)amino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino}methyl}imidazol-1-ylmethyl) benzonitrile,

10 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)propylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

15 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)butylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

20 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-2-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-2-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

25 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-3-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-3-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

30 (*R*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-4-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

35 (*S*)-4-(5-{{(1-Benzyl-2-oxopyrrolidin-3-yl)pyridin-4-ylmethylamino}methyl}imidazol-1-ylmethyl)benzonitrile,

- (*R*)-4-(5-{{(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 5 (*S*)-4-(5-{{(3-Aminopropyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{(2-Aminoethyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 10 (*S*)-4-(5-{{(2-Aminoethyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{(4-Aminobutyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 15 (*S*)-4-(5-{{(4-Aminobutyl)(1-benzyl-2-oxopyrrolidin-3-yl)amino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- 20 (*S*)-4-{5-[2-(1-Benzyl-2-oxopyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- 25 (*R*)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- (*S*)-4-{5-[2-(2-Oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- 30 (*R*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,

- (*S*)-4-{5-[2-(2-Oxo-1-phenethylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile,
- (*R*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 5 (*S*)-4-(5-{[1-(Naphthalene-1-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 10 (*R*)-4-(5-{[1-(Naphthalene-2-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- (*S*)-4-(5-{[1-(Naphthalene-2-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,
- 15 (*R*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- (*S*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile,
- 20 (*R*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide,
- (*S*)-*N*-(1-Benzoylpyrrolidin-3-yl)-2-[1-(4-cyanobenzyl)-1*H*-imidazol-5-yl]acetamide,
- (*R*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-[1-(naphthalene-1-carbonyl)pyrrolidin-3-yl]acetamide,
- 25 (*S*)-2-[1-(4-Cyanobenzyl)-1*H*-imidazol-5-yl]-*N*-[1-(naphthalene-1-carbonyl)pyrrolidin-3-yl]acetamide,
- 30 (*R*)-4-(5-{[1-(3-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl) benzonitrile,
- (*S*)-4-(5-{[1-(3-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl) benzonitrile,
- 35

(*R*)-4-{5-[(1-Benzoylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,

(*S*)-4-(5-{[1-(2-Chlorobenzoyl)pyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)
benzonitrile,

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(*R*)-4-(5-{[1-(2-Methylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{[1-(2-Methylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

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(*R*)-4-(5-{[1-(Isoquinoline-4-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

(*S*)-4-(5-{[1-(Isoquinoline-4-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

15

(*R*)-4-(5-{[1-(5-Bromopyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

20

(*S*)-4-(5-{[1-(5-Bromopyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl} imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[1-(2-Methylsulfanylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}
imidazol-1-ylmethyl)benzonitrile,

25

(*S*)-4-(5-{[1-(2-Methylsulfanylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}
imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[1-(2-Ethylsulfanylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}
imidazol-1-ylmethyl)benzonitrile,

30

(*S*)-4-(5-{[1-(2-Ethylsulfanylpyridine-3-carbonyl)pyrrolidin-3-ylamino]methyl}
imidazol-1-ylmethyl)benzonitrile,

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- 4-(5-{{(3*R*)-1-(*trans*-Cotinine-4-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 5 4-(5-{{(3*S*)-1-(*trans*-Cotinine-4-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(Biphenyl-2-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 10 (*S*)-4-(5-{{1-(Biphenyl-2-carbonyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 15 (*S*)-4-(5-{{1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- (*R*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenoxybenzonitrile,
- 20 (*S*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenoxybenzonitrile,
- 25 (*R*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile,
- (*S*)-4-(5-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)-2-phenethyloxybenzonitrile,
- 30 (*R*)-2-Benzyloxy-4-(5-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,
- 35 (*S*)-2-Benzyloxy-4-(5-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-ylamino}methyl} imidazol-1-ylmethyl)benzonitrile,

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile,

5 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-(3-phenylpropoxy)benzonitrile,

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile,

10

(*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile,

(*R*)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,

15

(*S*)-4-{5-[(2-oxo-1-pyridin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile,

20 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](3-phenylpropyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,

(*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](3-phenylpropyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,

25

(*R*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,

(*S*)-4-[5-({(3-Aminopropyl)[1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl]amino}methyl)

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imidazol-1-ylmethyl]benzonitrile,

(*R*)-*N*-(3-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,

- (*S*)-*N*-(3-{{1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl}[1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- 5 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 10 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-piperazin-1-ylethyl)amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 15 (*R*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][2-(pyridin-2-ylamino) ethyl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- (*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl][2-(pyridin-2-ylamino) ethyl]amino}methyl)imidazol-1-ylmethyl]benzonitrile,
- 20 (*R*)-6-Amino-*N*-(3-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl}[1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- 25 (*S*)-6-Amino-*N*-(3-{{1-(3-chlorobenzyl)-2-oxopyrrolidin-3-yl}[1-(4-cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}propyl)nicotinamide,
- (3*S*)-4-[5-({1-[(*S*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- 30 (3*S*)-4-[5-({1-[(*R*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- (3*R*)-4-[5-({1-[(*R*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino}methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- 35

- (3*R*)-4-[5-({ 1-[(*S*)-(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]-2-fluorobenzonitrile,
- 5 (3*S*)-2-Fluoro-4-[5-({ 1-[(*S*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- (3*S*)-2-Fluoro-4-[5-({ 1-[(*R*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- 10 (3*R*)-2-Fluoro-4-[5-({ 1-[(*R*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- (3*R*)-2-Fluoro-4-[5-({ 1-[(*S*)-(3-hydroxyphenyl)(phenyl)methyl]-2-oxopyrrolidin-3-ylamino } methyl)imidazol-1-ylmethyl]benzonitrile,
- 15 (3*R*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- (*R*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- 20 (*S*)-2-Fluoro-4-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-ylmethyl)benzonitrile,
- (*R*)-2-Fluoro-4-[1-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-yl)eth-1-yl]benzonitrile,
- 25 (*S*)-2-Fluoro-4-[1-(5- { [1-(7-hydroxynaphthalen-1-yl)-2-oxopyrrolidin-3-ylamino] methyl } imidazol-1-yl)eth-1-yl]benzonitrile,
- (*R*)-3- { [1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino } pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide,
- 30 (*S*)-3- { [1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino } pyrrolidine-1-carboxylic acid (adamantan-1-yl)amide,

(*R*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (2,6-difluorophenyl)amide,

5 (*S*)-3-{[1-(4-Cyanobenzyl)-1*H*-imidazol-5-ylmethyl]amino}pyrrolidine-1-carboxylic acid (2,6-difluorophenyl)amide,

(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile,

10 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}pyridin-3-ylmethyl)benzonitrile,

(*R*)-4-{5-[(2-Oxo-1-pyridin-4-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

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(*S*)-4-{5-[(2-Oxo-1-pyridin-4-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

(*R*)-4-{5-[(2-Oxo-1-pyridin-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

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(*S*)-4-{5-[(2-Oxo-1-pyridin-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

25 (*R*)-4-{5-[(2-Oxo-1-pyrazin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

(*S*)-4-{5-[(2-Oxo-1-pyrazin-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

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(*R*)-4-{5-[(2-Oxo-1-tetrahydrofuran-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

(*S*)-4-{5-[(2-Oxo-1-tetrahydrofuran-3-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile;

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- (*R*)-4-{5-[(2-Oxo-1-thiazol-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 5 (*S*)-4-{5-[(2-Oxo-1-thiazol-2-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(1-(4-Morpholinophenyl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 10 (*S*)-4-{5-[(1-(4-Morpholinophenyl)-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(1-(1-Benzylpyrrolidin-3-yl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 15 (*S*)-4-{5-[(1-(1-Benzylpyrrolidin-3-yl-2-oxopyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- (*R*)-4-{5-[(2-Oxo-1-quinolin-5-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 20 (*S*)-4-{5-[(2-Oxo-1-quinolin-5-ylpyrrolidin-3-ylamino)methyl]imidazol-1-ylmethyl} benzonitrile;
- 25 (*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}imidazol-1-ylmethyl)benzonitrile;
- (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}imidazol-1-ylmethyl)benzonitrile;
- 30 (*S*)-4-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole;
- 35 (*R*)-4-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methanoyl}-3-

(4-cyanophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole,;

(*R*)-2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile;

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(*S*)-2-Fluoro-4-{5-[2-(2-oxo-1-phenylpyrrolidin-3-ylamino)ethyl]imidazol-1-ylmethyl} benzonitrile;

(*R*)-4-(5-{[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]ethyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile;

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(*S*)-4-(5-{[1-(2-Bromo-5-methanesulfonyloxybenzyl)-2-oxopyrrolidin-3-ylamino]ethyl}imidazol-1-ylmethyl)-2-fluorobenzonitrile;

(*R*)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine;

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(*S*)-3-{[1-(4-Cyanobenzyl)imidazol-5-yl]methylamino}-1-[(2-ethoxybenzyl)oxycarbonyl]pyrrolidine;

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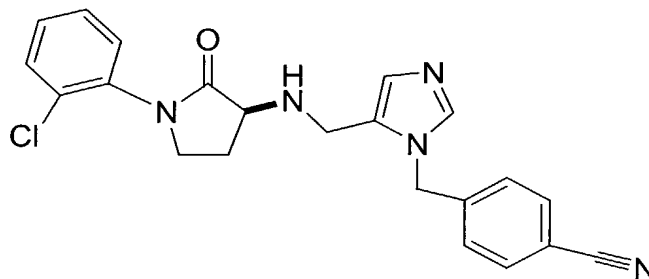
(*R*)-3-{[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine;

(*S*)-3-{[1-(4-Cyanobenzyl)-2-methylimidazol-5-yl]methylamino}-1-[(2-trifluoromethoxybenzyl)oxycarbonyl]pyrrolidine;

25

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

8. The compound according to Claim 7 which is:



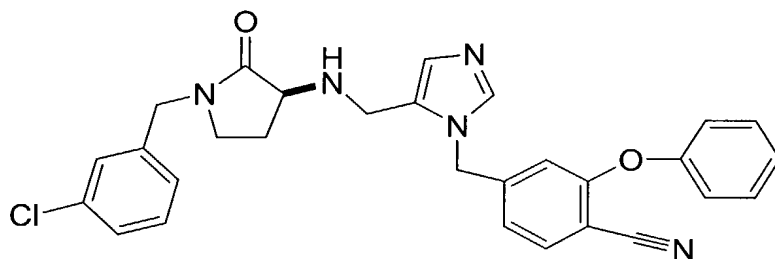
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(*S*)-4-(5-{[1-(2-Chlorophenyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)benzonitrile

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

5

9. The compound according to Claim 7 which is:

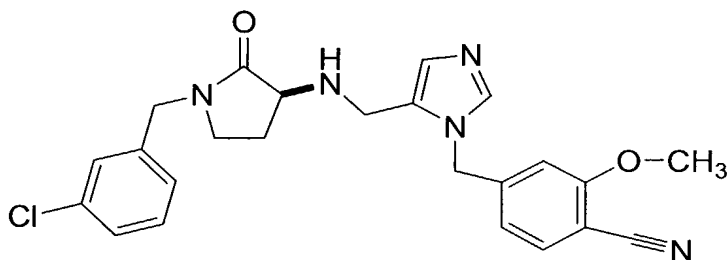


(*R*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-phenoxybenzonitrile

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or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

10. The compound according to Claim 7 which is:

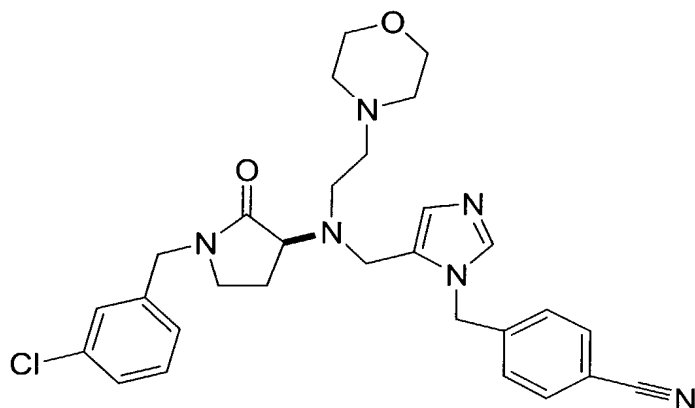


15 (*S*)-4-(5-{[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-ylamino]methyl}imidazol-1-ylmethyl)-2-methoxybenzonitrile

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

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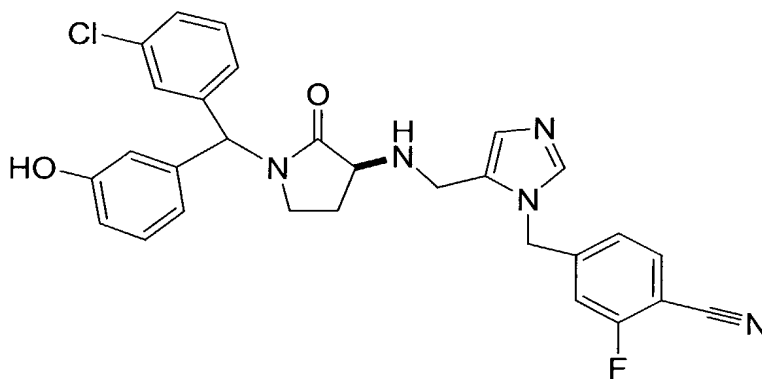
11. The compound according to Claim 7 which is:



(*S*)-4-[5-({[1-(3-Chlorobenzyl)-2-oxopyrrolidin-3-yl](2-morpholin-4-ylethyl)amino} methyl)imidazol-1-ylmethyl]benzonitrile

5 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

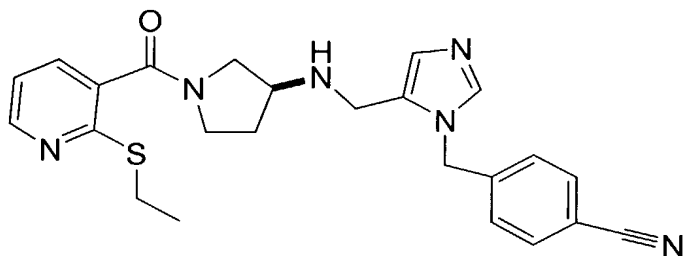
12. The compound according to Claim 7 which is:



10 (*3S*)-4-[5-({1-[(3-Chlorophenyl)(3-hydroxyphenyl)methyl]-2-oxopyrrolidin-3-yl}amino) methyl]imidazol-1-ylmethyl]-2-fluorobenzonitrile

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

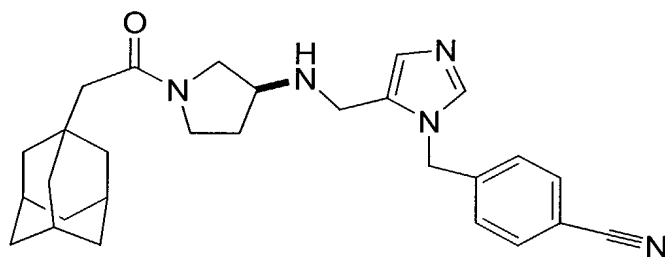
13. The compound according to Claim 7 which is:



4-(5-([(3*S*)-1-(2-Ethylsulfanylpentidine-3-carbonyl)pyrrolidin-3-ylamino]methyl)imidazol-1-ylmethyl)benzonitrile

5 or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

14. The compound according to Claim 7 which is:



10 (*S*)-4-(5-([1-(Adamantan-1-ylacetyl)pyrrolidin-3-ylamino]methyl)imidazol-1-ylmethyl)benzonitrile

or a pharmaceutically acceptable salt, an optical isomer or stereoisomer thereof.

15 15. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

20 16. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

17. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

5 18. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 7.

10 19. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

15 20. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 2.

20 21. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 3.

22. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 7.

25 23. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

30 24. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 2.

35 25. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 3.

26. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 7.

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27. A method for treating neurofibromen benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

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28. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

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29. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

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30. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

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31. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1.

32. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

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33. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

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34. A method of conferring radiation sensitivity on a tumor cell using a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

35. A method of treating cancer using a therapeutically effective amount of a compound of Claim 1 in combination with an antineoplastic.
- 5 36. A method according to Claim 33 wherein the antineoplastic is paclitaxel.

SEQUENCE LISTING

<110> Merck & Co., Inc.
 Bell, Ian M.
 Beshore, Douglas C.
 Gallicchio, Steven N.
 Lumma, William C.
 Sisko, John T.
 Zartman, C. Blair

<120> INHIBITORS OF PRENYL-PROTEIN TRANSFERASE

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 <151> 1999-09-09

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/24542**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : Please See Extra Sheet.

US CL : 548/314.7; 546/275.1, 157; 544/139, 370; 514/397, 341, 314, 255.05, 235.8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/314.7; 546/275.1, 157; 544/139, 370; 514/397, 341, 314, 255.05, 235.8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts Index Chemicus

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

None

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,756,528 A (ANTHONY et al.) 26 May 1998, see entire document. | 1-36 |
| A | US 5,939,557 A (ANTHONY et al.) 17 August 1999, see entire document. | 1-36 |

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

*

Special categories of cited documents:

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

A

document defining the general state of the art which is not considered to be of particular relevance

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

E

earlier document published on or after the international filing date

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

L

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O

document referring to an oral disclosure, use, exhibition or other means

P

document published prior to the international filing date but later than the priority date claimed

&

document member of the same patent family

Date of the actual completion of the international search

30 NOVEMBER 2000

Date of mailing of the international search report

08 JAN 2001

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/24542

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07D 403/02, 215/20, 401/02; A61K 31/4178, 31/496, 31/4439, 31/4709, 31/454; 31/5355